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THE AMERICAN HEART JOURNAL

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The American Heart Journal

VOL. IX DECEMBER, 1933 No. 2

Original Communications

THE NATURE OF THE VASCULAR COMMUNICATIONS BETWEEN THE CORONARY ARTERIES AND THE CHAMBERS OF THE HEART*†‡

JOSEPH T. WEARN, M.D., STACY R. METTIER, M.D.,
THEODORE G. KLUMPP, M.D., AND LOUISE J. ZSCHIESCHE, A.B.
CLEVELAND, OHIO

THE existence of direct vascular communications between the coronary arteries and the chambers of the heart has been claimed and denied. Such evidence as has been presented in favor of the existence of these channels has been indirect and based largely upon experiments in which perfusions and injections of the coronary vessels were employed. The use of the same general methods variously modified has led others to deny the existence of channels between the coronary arteries and the heart chambers. If such channels do exist they almost certainly play a rôle in the circulation of the heart, but at the present time there is no agreement as to the nature or the importance of that rôle. It seemed wise, therefore, to study the vessels by injections and by the rather tedious method of serial sections and wax-plate reconstructions in order to establish their anatomical and histological structure. Such knowledge, if established, should be of definite value to those investigators who, in studying the physiology of the coronary circulation, have been compelled to make one of two assumptions; namely, that vascular channels between the coronary arteries and the atria and ventricles either do or do not exist.

*From the H. K. Cushing Laboratory of Experimental Medicine in the Department of Medicine of Western Reserve University School of Medicine and Lakeside Hospital, Cleveland, Ohio, and from the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School.

†The results reported in the first part of this paper (celloidin injection experiments) were carried out in 1928 while Dr. Mettier was working with me in the Thorndike Laboratory. The investigation has since been extended and completed in the H. K. Cushing Laboratory where Dr. Klumpp joined in the work. Miss Zschiesche assisted in the investigation throughout. J. T. W.

‡The expenses of this investigation have been defrayed in part by a grant from the B. F. Bourne Memorial Fund of the Department of Medicine, Western Reserve University.

It is proposed to present here histological and other evidence of the existence of direct vascular channels between the coronary arteries and the chambers of the heart, as well as the results of certain observations upon the histological nature of these communicating vessels.

The belief that the coronary arteries have direct vascular communications with the chambers of the heart is not a new one. The idea was first advanced by Raymond Vieussens in 1705 in a letter to Monsieur Boudin, Conseiller d'Etat, Premier Medicin de Monseigneur le Dauphin. Boudin's reply in which he acknowledged receipt of Vieussens' letter was dated July 9, 1705. Vieussens' letter was published in 1706.[1] In it he related how, in examining the depth of the roots of a large polyp which had formed in the right ventricle of the heart of a man who had died of a slow fever accompanied by violent palpitation of the heart, he traced the firmest roots of the clot as far as certain holes which seemed to him to be the orifices of specific ducts. He made several similar observations and from them concluded that blood circulating in the medial and inner fleshy vessels of the heart was carried into the cavities by the ducts in which the polyps first take root. Next he injected saffron dye, dissolved in spirits, into the left coronary artery and observed its passage into the left atrium and left ventricle, but none escaped via the veins into the right chambers. He called these communicating vessels "fleshy" ("le reste est poussé en partie dans le ventricule gauche de ce viscere par des vaisseaux, que j'appelerai charnus cy-aprés"). Vieussens also dissected human hearts and the hearts of sheep and calves, and, with the aid of a microscope, found the small openings (ouvertures) in the chambers of all, in some instances with delicate valves over the openings while in others valves were lacking. He noted that many of the channels (conduits) received blood from several fleshy vessels. To these he gave the name "common vessels" and to their orifices the name "common openings" ("je les appelleray des vaisseaux communs: j'appelleray aussi leurs embouchures des ouvertures communes").

These vessels and openings, so clearly described by Vieussens, have since been confused with somewhat similar ones described by Thebesius[2] two years later in 1708, and as a result all such vessels are now commonly known as thebesian veins. Thebesius injected certain substances into the coronary veins and noted their escape into the heart cavities through small openings in the endocardium. He was familiar with Vieussens' work and so states in his paper.

Thebesius' belief that the vessels were connected only with veins was supported by several anatomists of the day and Vieussens' work was soon forgotten. Lancisi[3] in 1740 injected mercury into the coronary arteries and observed its appearance in the heart chambers, but believed with Thebesius that it escaped through venous channels (thebesian veins). In 1798 John Abernethy,[4] by making a "common coarse waxen

injection'' into the coronary arteries, observed that it flowed readily into the cavities of the heart. He also injected masses of a different color into the arteries and veins and concluded that vessels from arteries and veins communicated with the heart chambers ''because the injection which was employed was too coarse to pass from one set of vessels to the other, and yet the different colored injections passed into the cavities of the heart unmixed.''

Then followed a period that might be termed the dark ages for the ''vaisseaux charnus'' and the thebesian veins, but it came to an end with the work of F. H. Pratt[5] in 1898 who, by means of perfusion of defibrinated blood through the ventricle of a cat's heart, kept it beating for an hour. This very important work furnished the first experimental evidence that the thebesian vessels might serve as an entrance for blood from the ventricles into the capillaries.

In 1928, Wearn[6] perfused the coronary arteries of human hearts with India ink and observed that the perfusate for the most part escaped into the chambers of the heart through the thebesian vessels. Histological sections of these hearts revealed the fact that very few, and in many instances scarcely any, of the capillaries contained ink particles. Moreover, when a celloidin mass too thick to pass through capillaries was injected into the coronary arteries, celloidin plugs were found protruding from small openings in the endocardial walls of the atria and ventricles, while the capillary bed remained uninjected. From these experiments the conclusion was drawn that direct vascular communication existed between the coronary arteries and the heart chambers. F. H. Pratt[7] has also observed plugs of gelatin protruding from the thebesian openings after injection of this thick mass into the coronary arteries. Mettier, Zschiesche, and Wearn[8] in 1929, and Wearn, Klumpp, and Zschiesche[9] in 1932 published the preliminary results of some experiments which are reported in full in this paper.

Grant and Viko[10] in 1929 injected the thebesian vessels through their endocardial foramina and through the coronary vessels. They used finely drawn glass cannulas of such sizes as to fit snugly into the endocardial foramina. Their injection pressure was produced by blowing from the mouth into the injection system. By this means a pressure of about 50 to 60 mm. Hg was obtained. They were able to confirm the existence of anastomoses between thebesian vessels and coronary veins and described several types of venous anastomoses. They also injected the coronary arteries but failed to find evidence of direct arterial communications and concluded that ''the coronary arteries communicate with the thebesian vessels only through capillaries.''

Stella[11] in 1931 employed the denervated heart-lung preparation in dogs in an attempt to test the claim of the existence of communications between the arteries and heart cavities by a physiological method. He

was able to maintain the pressure within the ventricles and drop the pressure within the coronary arteries and, since under such conditions he was unable to demonstrate back-flow from the chambers into the arteries, he concluded that his work did not support the existence of large channels connecting the thebesian veins with the coronary arteries.

Grant[12] in 1926 found in a child's heart, which presented a congenital anomaly, persistent channels communicating freely with the heart cavities and with the coronary arteries, veins, and capillaries. Bellet, Gouley, and McMillan[13] in 1933 reported dilated sinusoids or thebesian veins in a heart which showed an advanced tuberculous fibrocaseous infiltration.

In view of the lack of agreement on the existence of vascular connections between the coronary arteries and the heart chambers, the experiments reported in this paper were devised and carried out.

METHODS AND OBSERVATIONS

Human hearts obtained at necropsy were used in the experiments reported in this study. No effort was made to select normal or abnormal hearts. Hearts were accepted for injection whenever they could be obtained from the necropsy table. The causes of death covered a wide range, but it so happened that none of the hearts showed any gross evidence of any pathological process.

The use of thick celloidin as an injection mass offered a method of approach in determining the presence and constancy of arterial communications with the heart chambers. In a previous experiment[6] it was found that celloidin could be prepared in a suspension sufficiently thin to pass through arteries and arterioles but too thick to penetrate the capillaries. The injection mass consisted of a 5 per cent solution of celloidin in acetone. A blue fluid mass was obtained by mixing crystal violet and brilliant green with the celloidin, and a red fluid mass was made by the addition of alkanin to the celloidin.[14] The red celloidin mass was used in making a cast of the ventricular chambers, and the blue for casting the coronary arteries. The following experiment is a typical one and illustrates the method:

PROTOCOL

Heart 10. Male. Aged thirty-two years. Death was the result of staphylococcus septicemia. The heart was placed in the ice box for twenty-four hours to allow for the passing off of rigor mortis, following which it was gently massaged in warm salt solution to break the remaining rigor and to remove all blood clots in the chambers. The coronary sinus and the tricuspid valve were closed by purse-string sutures. (In some instances the valve leaflets were everted and clamped.) A cannula was tied into each coronary artery and into the pulmonary artery. The red celloidin mass was injected through the cannula in the pulmonary artery into the right ventricle at a pressure of 160 mm. Hg, and this pressure was maintained until the experiment was completed. At the same time, suction was applied to the

Fig. 1.

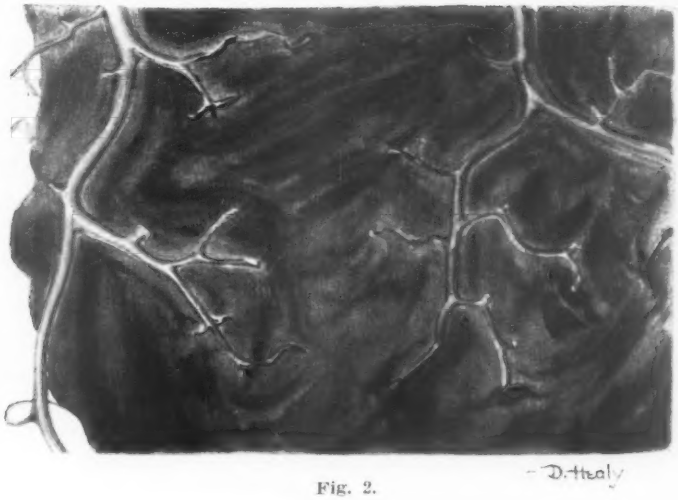

Fig. 2.

Plate 1

Fig. 1.—Heart 10. The painting shows a red celloidin cast of the chamber of the right ventricle and a blue celloidin cast of the coronary arteries. The outer branches of the arteries have been removed in order to show the red tips at the junctions of the coronary arteries and the red cast of the chamber. The artery tips are firmly fused with the celloidin cast of the right ventricular cavity (see Protocol of Heart 10).

Fig. 2.—Heart 10. A painting on a larger scale to show more clearly the red tips at the points where the casts of the coronary artery fuse with the cast of the right ventricular cavity (see Protocol of Heart 10).

UNIV. OF MICH.

cannulas in the coronary arteries. After a lapse of ten minutes the suction was discontinued, care being taken to prevent the entrance of air, and the blue mass was injected into the coronary arteries at a pressure of 180 mm. Hg. This pressure was maintained for fifteen minutes, after which the cannulas were clamped off and the heart was plunged immediately into ice water where it remained for forty-eight hours to permit maceration of the muscle. The heart was then placed in 75 per cent HCl for seventy-two hours, during which time the acid was changed twice. This usually completed maceration of the muscle. The cast was washed free of muscle by playing a very fine stream of water on the débris. (Extreme care was necessary in this procedure to avoid breakage of the finer vessels.) After washing, the cast was mounted.

A reproduction of a painting of this specimen is shown in Plate I, Figs. 1 and 2, and a photograph of the same specimen in Plate II, Fig. 1. The specimen consists of a solid red cast of the chamber of the right ventricle and blue casts of the anterior branches of the right and left coronary arteries. It is to be noted that some of the terminations of the branches of the anterior branch of the right coronary artery are red in color. These red tips vary from 4 to 15 mm. in length. The distal ends are continuous with the red mass in the ventricles, and the proximal ends fuse smoothly with the blue mass in the arteries. Such vessels when grasped between the fingers or with forceps are found to be firmly attached by this red tip to the ventricular mass, showing complete fusion of the two celloidin masses. The cast of the vessels is smooth and round and shows no lateral communications. Capillaries are not injected. It is evident, therefore, that the red celloidin mass has found its way directly from the right ventricle into the terminations of the right coronary artery, as shown by its fusion with the blue mass injected into the artery at its origin. The pressure within the right ventricle probably aided in the entrance of the red mass into the ends of the branches of the coronary arteries.

Fifteen human hearts were injected according to the technic described in the preceding protocol. In all of the final specimens red tipped terminations of arteries fused to the ventricular mass were found. The number of these vessels in each heart varied with the completeness of the injection and with the degree of damage that occurred during the washing process. A composite of all of the specimens injected would average about twenty to twenty-five communicating arteries scattered generally over the heart walls. It is not felt that these figures represent the total number of communications, for in many instances it was obvious that the injection was incomplete.

These communicating vessels between the coronary arteries and the ventricles usually had their origin from the main trunks of the coronary arteries during their course toward the apex of the heart. Many of the deeper branches of the arteries lying near the endocardium also gave off frequent branches. As many as eight to ten communicating branches were frequently seen in the course of the anterior branch of the left

Fig. 1. Fig. 2.

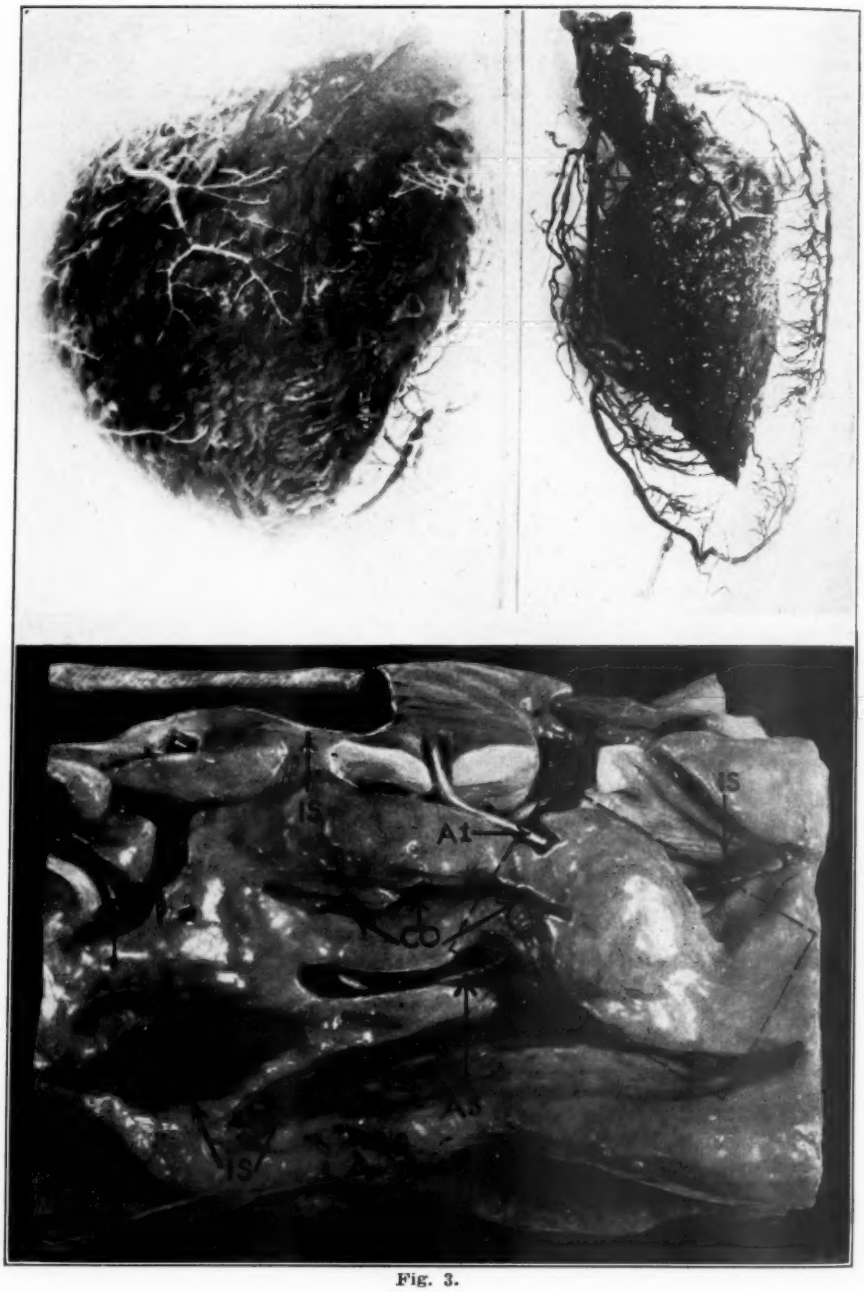

Fig. 3.

Plate II.

Fig. 1.—Heart 10. A photograph of the same specimen shown in the painting in Plate I, Figs. 1 and 2.

Fig. 2.—Heart 9. A celloidin cast of the right ventricular chamber and the coronary arteries. It shows firm fusion of the tips of some of the arteries with the cast of the chamber.

(See opposite page for explanation of Fig. 3.)

coronary artery from the base to the apex, and several openings were usually found near the apex of the ventricles. In one specimen in which both ventricles were injected, communicating vessels passed from the left anterior coronary artery to both chambers. From six to eight vessels were found with great regularity in the upper two-thirds of the anterolateral surface of the right ventricle. They have not been demonstrated with as great a frequency on the posterior surface of the heart, but in one well-injected specimen there were six entering the right ventricle posteriorly. Many of these vessels terminated not only on the surface of the columnae carneae, as represented by the depressions in Plate I, Figs. 1 and 2, and in Plate II, Fig. 1, but in the intercolumnar spaces as well.

In order to determine the relation of the arterial terminations to those of the veins a heart was prepared in the following manner:

PROTOCOL

Heart 11. Male. Aged thirty-four years. Died of pneumonia. The heart was placed in the ice box for forty-eight hours and then washed and massaged in the usual manner. A cannula was tied into each coronary artery; one in the pulmonary artery and one in the coronary sinus. The tricuspid valve was closed and made water-tight with an Ochsner clamp. A red celloidin mass was injected into the right ventricle at a pressure of 160 mm. Hg and suction was applied to the cannulas in the coronary arteries and in the coronary sinus. After fifteen minutes the suction apparatus was removed in such a manner as to prevent the entrance of air, and the blue mass was injected into the arteries and into the coronary sinus. Some of the dye escaped from the veins into the atria. Pressure was released at the end of fifteen minutes and the heart was plunged into ice water. The specimen was macerated and mounted by the technic described in the preceding protocol.

The specimen consisted of a solid red celloidin cast of the chamber of the right ventricle. Study of this specimen showed not only the red tips to the arteries as previously described, but in addition, several small red tips to the veins which were firmly fused with the blue mass in the veins, thus providing direct evidence of venous communication with the ventricular chambers. This finding of venous connections with the ventricles was in agreement with former work[6] in which serial sections demonstrated direct communication between thebesian vessels and the coronary veins.

The evidence for the existence of communicating vessels between the coronary arteries and the heart chambers in fifteen consecutive hearts

Plate II (Continued). Fig. 3.—Heart 23 Kb. A photograph of a wax-plate reconstruction of a section of the left ventricular wall near the apex, in which is shown the common opening (CO) through which several "arterio-luminal" vessels and "myocardial sinusoids" open into the lumen of the ventricle. Several intertrabecular spaces (IS) are shown. The wax has been dissected away to show the arteries (A_1, A_2, and A_4) which communicate with the cavity through the common opening. The dotted rectangle includes the tissue from which serial sections shown in Plate III, Fig. 2, and Plates IV, V, and VI were cut. Structures shown in this figure and in Plates III, IV, V, and VI are from the same heart and are designated identically for comparison. This photograph has been reduced to approximately three-fifths of the size of the original model which was constructed on a magnification of 20 times the original block of tissue.

seemed conclusive. Vieussens[1] called these vessels "vaisseaux charnus" or fleshy vessels. His reason for so designating them, however, was based upon a misconception. He believed that the myocardium was made up of vessels springing from the coronary arteries "as hairs from a wig" and he made no distinction between the vessels and the muscle fibers. For the sake of clarity and to avoid confusion, this group of vessels will henceforth be referred to in this paper as "arterio-luminal" vessels. This term is suggested inasmuch as they run from the coronary arteries into the lumen of the heart. For those connecting vessels between the coronary arteries and the atria the term "arterio-atrial" vessels might be used, and similarly for those between the coronary arteries and the ventricular chambers the term "arterio-ventricular" vessels might be employed.

Inasmuch as the structure of such vessels had never been described, the next step in the study was obvious. Moreover, it was felt that, if one of these vessels could be identified in the intact heart wall, a block of tissue containing it could be removed, sectioned serially and reconstructed. Such a study, if carried out successfully, should answer the possible criticisms that the connections shown in the celloidin casts were due to artifacts. In addition, it should establish beyond question the arterial origin of the communications and reveal the histological structure of the vessels themselves.

In approaching this task, several difficulties were encountered which necessitated a change in the injection mass employed. It was a simple matter to identify the celloidin plugs protruding from the openings of the "arterio-ventricular" communicating vessels, but, in the course of fixation, dehydration, mounting, and staining, the celloidin was dissolved and the vessels could not be traced. In order to overcome this difficulty, a suspension of Berlin blue in gelatin* was selected as an injection mass. A few experiments revealed, however, that this mass penetrated the capillaries and thus made it extremely difficult to follow the "arterio-luminal" communicating vessels. A method had to be devised, therefore, which would keep the gelatin from entering the capillaries. It was necessary of course to carry out the gelatin injections at a temperature slightly above the solidifying point of gelatin. This was accomplished by immersing the heart, injection bottle, and connecting tubing in a tank of water at the proper temperature. It was found that the introduction of cold salt solution into the ventricles at the appropriate time caused a chilling of the myocardium which allowed the gelatin to flow through the arteries and arterioles but aided in the prevention of its entrance into the capillaries. Under such conditions, it

*The injection mass was made up as follows: Soak 100 grams of Silver Label gelatin (Michigan Carbon Works) for two hours in 150 c.c. of distilled water. Warm over a water-bath until the gelatin dissolves, then add 5 grams of Berlin blue suspended in 100 c.c. of distilled water and thoroughly mix. Add 1 gram of thymol and filter the mass through several thicknesses of gauze.

was possible to inject the "arterio-luminal" communicating vessels without filling the capillary bed. When the heart was opened, solid gelatin plugs were found protruding from the endocardial openings of the channels, the gelatin having solidified on contact with the chilled salt solution in the ventricular cavities.

A block of heart muscle containing the opening, from which the gelatin protruded, was excised and placed under a binocular bi-objective dissecting microscope where the opening was identified and marked with India ink. The tissue block was then fixed and imbedded in paraffin preparatory to cutting serial sections. The following protocol illustrates the method:

PROTOCOL

Heart 23 Kb. Aged thirty-five years. Death resulted from lobar pneumonia. Heart weight 440 gm. (This weight was recorded before large clots were removed from the cavities.) This experiment was started forty hours post-mortem. Blood clots were removed from the ventricles so far as was possible. The coronary sinus and posterior great veins were tied off near their entrance to the right atrium. The coronary arteries were cannulated. Rubber tubing was led into the left and right ventricles through the aorta and the pulmonary artery respectively for the purpose of introducing chilled salt solution into these cavities. The aorta and pulmonary artery were closed by filling the space around the rubber tubing with cotton. The atrio-ventricular valves were then closed by placing cotton pledgets in their openings. These steps were taken in order to seal the ventricular chambers, thereby preventing the entrance into them of gelatin from any source other than from the openings in their own walls. The coronary cannulas and the rubber tubing connecting them with the bottle of injection mass were warmed and filled with gelatin after the removal of all air. The heart and injection apparatus were then placed in a water-bath at a temperature of 25° C. preparatory to starting the injection. The temperature of the gelatin was 53° C. Physiological salt solution chilled to a temperature of −2° C. was introduced into the ventricles in sufficient quantity to fill the chambers. After a lapse of approximately one or two minutes, the injection of Berlin blue gelatin into the coronary arteries was begun. The flow soon ceased but the injection pressure of 220 mm. Hg was maintained for about five minutes.

After sufficient time had elapsed to allow for solidification of the gelatin, the heart was opened with great care in order to prevent the entrance of any gelatin from the outside. The cotton pledgets in the atrio-ventricular valves, as well as those in the aorta and pulmonary artery, were inspected and removed. No leakage of gelatin into the ventricles had occurred.

Inspection of the myocardium showed an excellent injection of the main arteries and arterioles. That part of the heart muscle which received most of its blood supply from the left coronary artery showed some capillary injection immediately beneath the pericardium where the muscle had not been chilled. There was no evidence of capillary injection in the muscle supplied mostly by the right coronary artery.

Blocks of the heart wall showing gelatin protruding from the endocardial openings were removed from the following positions for study:

1. Right ventricle: Septal wall, halfway between pulmonary valve and apex.

2. Left ventricle: At the apex from a pocket formed by the junction of two trabeculae. (It is from this tissue that the reconstructions shown in Plate II, Fig. 3, and Plate III, Fig. 1 were made.)

The tissue removed from the left ventricle in the experiment just described was fixed, imbedded in paraffin, cut into serial sections eight micra thick, mounted and stained with van Gieson's stain. Careful study of these sections revealed convincing evidence of direct communications between the coronary arteries and the chambers of the ventricles.

Inasmuch as these communicating channels frequently ran through many of the histological sections, it was obviously impossible to publish photographs of all the sections. All sections were cut eight micra thick and for this reason sharp photomicrographs could not be obtained in each instance. It was felt, therefore, that the vessels should be reconstructed, inasmuch as such a procedure would submit our microscopic observations to a further test of accuracy. In carrying out the reconstruction, it was our good fortune to have the constant guidance and criticism of Dr. Bradley M. Patten of the Department of Histology in the School of Medicine of Western Reserve University. Dr. Patten's wide experience in this field made his advice and help invaluable.

A reconstruction in wax (Plate II, Fig. 3) was made of the block of myocardium according to the Born wax-plate reconstruction method in order to show the gross relationship of the arteries to the common opening* in the endocardium and to determine whether the common opening, into which the communicating vessels opened, connected with other intertrabecular spaces. This model was constructed on a scale twenty times the size of the original block of tissue. Its purpose was to show only gross relationships which might serve as guides in the construction of a second model of greater magnification. The wax has been dissected away in order to bring the arteries into view. Reference to the figure (Plate II, Fig. 3) will show three arteries lying in close proximity to the common opening from which the gelatin plug protruded before its removal in the process of imbedding. Branches from all three of the arteries shown opened into the common opening, and the common opening itself was found to communicate with three other intertrabecular spaces shown in the model. The lettering of the structures in the figure (Plate II, Fig. 3) is identical with that used for all other plates of the same heart (H 23 Kb) and is so arranged that the same structure is designated by the same letter in Plates III, IV, V, and VI. For instance, A_1 represents the same artery in each of these plates.

*The term "common opening" is used in the sense that Vieussens used it, namely, to indicate an inpocketing of the endocardium into which several vessels opened.

Plate III. Fig. 1.—Heart 23 Kb. Photograph of a wax-plate reconstruction of the "arteriosinusoidal" vessels and the "myocardial sinusoids" in the block of tissue shown within the broken lines in Plate II, Fig. 3. The structures shown in the model represent reconstructions of the lumina of the vessels. For instance, A_1 is an artery, AS_1 is a branch of the artery which empties directly into the common opening (CO) which is an inpocketing of the endocardium of the left ventricle. A_1 and CO, for instance, are shown in Plate II, Fig. 3, and are labeled identically. This wax-plate reconstruction was made on a scale of 200 times the original. This photograph is approximately one-fifth of the actual size of the model.

Fig. 2.—Heart 23 Kb. A photograph of one of the serial sections from which the model in Fig. I of this plate was reconstructed. The various structures in this figure are designated identically with those in Fig. 1. END = endocardium. MS = "myocardial sinusoid." CO = common opening. AS = "arterio-sinusoidal" vessel. A = artery. OMS = opening of a "myocardial sinusoid" into the lumen of the ventricle. Numbers appearing after letters enable one to identify the same structures in Plate II, Fig. 3, and Plates III, IV, V, and VI. (×41)

Fig. 1.

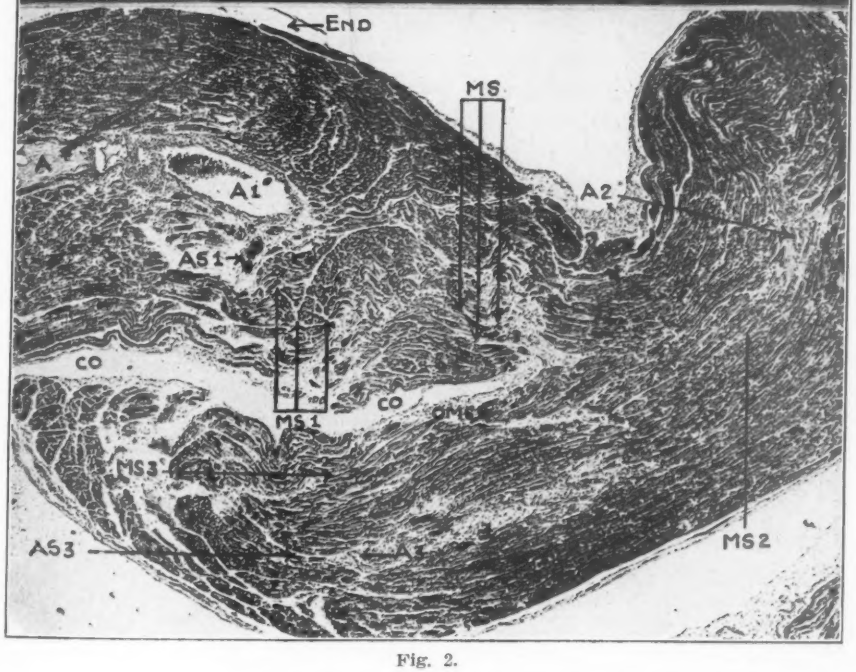

Fig. 2.

Plate III.

(See opposite page for explanation of Figs. 1 and 2.)

In one particular part of the block of myocardium which was used in making the serial sections, a number of arterial branches were found which communicated with the lumen of the ventricle via the common opening. This area is indicated by the dotted rectangle in Plate II, Fig. 3. It was found that several communicating vessels lay within this small space; consequently, it was selected for a second reconstruction. In carrying out this reconstruction, the lumina of the blood vessels and of the intertrabecular space were reconstructed so that in the final state the model represented a cast of the cavities of the blood vessels and their openings into the lumen of the ventricle through a common opening. The drawings used in the reconstruction of this model were made from projections of the individual sections at a magnification of 200 diameters. Plate III, Fig. 2 is a low power photomicrograph of one of the sections used in the reconstruction of the model shown in Plate III, Fig. 1.

Completion of the model of the vessels furnished confirmation for our microscopic observations. Moreover, the careful study of the sections which was necessary for accurate reconstruction brought to light two distinct groups of vessels which serve as communicating channels between the arteries and the heart chambers. A vessel of the first group is usually a small branch of a coronary artery which gradually loses its arterial character through changes in its wall due to the loss of the media, thinning of the intima, and a gradual disappearance of the adventitia. Such a vessel breaks up into channels whose lumina are very irregular. The walls of these channels are very thin and are made up of endothelium only or of endothelium reinforced by a minimal amount of subendothelial connective tissue. The diameters of these channels may vary from 50 to 250 micra. The characteristics of these vessels are identical with those of sinusoids as described by Minot[15] in 1900. Their walls lie in close contact with the heart muscle, running between bundles of muscle fibers and at times between the fibers themselves. Hereafter, in this paper these channels will be referred to as "myocardial sinusoids." The arterial branches which supply the sinusoids will be referred to as the "arterio-sinusoidal" vessels. Such a name indicates the origin and the distribution of the vessels. An "arterio-sinusoidal" vessel is shown in Plate V, Figs. 1, 2, 3, and 4. A "myocardial sinusoid" is also shown in Plate V, Figs. 4 and 5. The fact that the wall of the "arterio-sinusoidal" vessel is arterial in character at the beginning and gradually changes to that of a simple endothelial tube of irregular lumen and diameter makes it inadvisable to call it either artery or vein. It can be differentiated with ease from

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Plate IV. Fig. 1.—Heart 23 Kb, section 139. The branching of the artery (A_1) is shown. The branch (AS_1) divides into "myocardial sinusoids" (MS_1) which empty into the common opening (CO) at (OMS_1). See Fig. 2. (×361)

Fig. 2.—Heart 23 Kb, section 142. Shows the opening of the "myocardial sinusoid" (MS_1) into the common opening (CO). (×340)

Fig. 3.—Heart 23 Kb, section 137. Shows a section of the "arterio-sinusoidal" vessel (AS_1). The wall of the artery (A_1) from which it arises is shown.

Fig. 1.

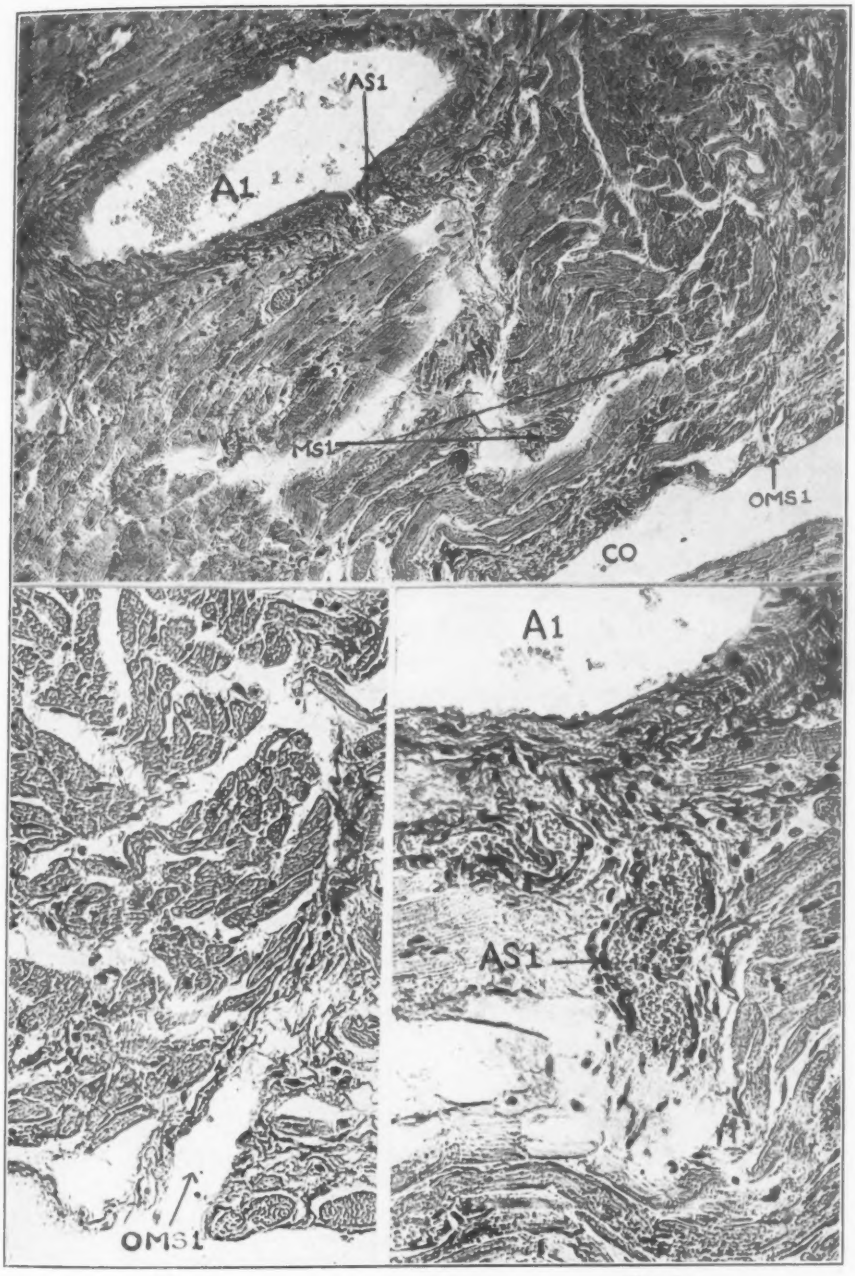

Fig. 2. Fig. 3.

Plate IV.

(See opposite page for explanation of Figs. 1, 2, and 3.)

a capillary by its much greater diameter and by its irregular lumen. The "arterio-sinusoidal" vessels may lose their arterial character immediately after branching from the artery (Plate V, Figs. 3 and 4). At times these vessels may give off a branch which divides into capillaries.

The "myocardial sinusoids" run a meandering course, anastomose very freely with one another and not infrequently with capillaries, and open into the lumen of the ventricle either directly or through a common opening. The model (Plate III, Fig. 1) illustrates the origin of the "arterio-sinusoidal" vessels. It also shows the anastomosing "myocardial sinusoids" and their openings into the common opening which is a simple inpocketing of the endocardium (Plate III, Fig. 1). In some instances, the "myocardial sinusoids" may run a direct course from the "arterio-sinusoidal" vessel to the lumen of the ventricle. (See Plate III, Fig. 1, A2 and MS2, and Plate VI, Figs. 1 and 2.)

When closed and empty, the "myocardial sinusoids" resemble closely and are easily mistaken for strands of fibrous tissue. One frequently finds a "myocardial sinusoid" cut longitudinally with small pockets of erythrocytes here and there to identify it as a vessel. Between the pockets of erythrocytes the walls may lie against one another and resemble somewhat similar structures in the bone marrow.

The similarity of the walls of the "myocardial sinusoids" to those of capillaries and the somewhat similar distribution between, and in close contact with, muscle bundles and muscle fibers would indicate that the "myocardial sinusoids" play a definite rôle in supplying parts of the heart with blood.

The second type of communicating vessels observed ran much more directly from the coronary arteries to the lumen of the ventricle. These vessels were similar to and undoubtedly identical with the "arterio-luminal" vessels described earlier in this paper and reproduced in Plate I, Figs. 1 and 2, and Plate II, Figs. 1 and 2. The finding and identifying of the "arterio-luminal" vessels by histological methods and the tracing of their course from the artery to the heart lumen by reconstruction are confirmatory of the experiments in which celloidin injections were employed and which were described earlier in this report. Two photomicrographs of "arterio-luminal" vessels are shown in Plate

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Plate V. Fig. 1.—Heart 23 Kb, section 183. Shows the branching of an "arterio-sinusoidal" vessel (AS_3) from an artery (A_3). (×410)

Fig. 2.—Heart 23 Kb, section 180. Shows the artery (A_3) and the "arterio-sinusoidal" vessel (AS_3). Note the thickness of the wall. (×372)

Fig. 3.—Heart 23 Kb, section 152. Shows the artery (A_3) at the extreme right edge of the figure and the "arterio-sinusoidal" vessel which has divided (AS_3) at the left. (×270)

Fig. 4.—Heart 23 Kb, section 137. Shows the "arterio-sinusoidal" vessel (AS_3) with the wall much thinner. At the right of the section a "myocardial sinusoid" (MS_3) is shown. (×410)

Fig. 5.—Heart 23 Kb, section 133. Shows the "myocardial sinusoid" (MS_3) into which the "arterio-sinusoidal" vessel (AS_3) opened. (×410)

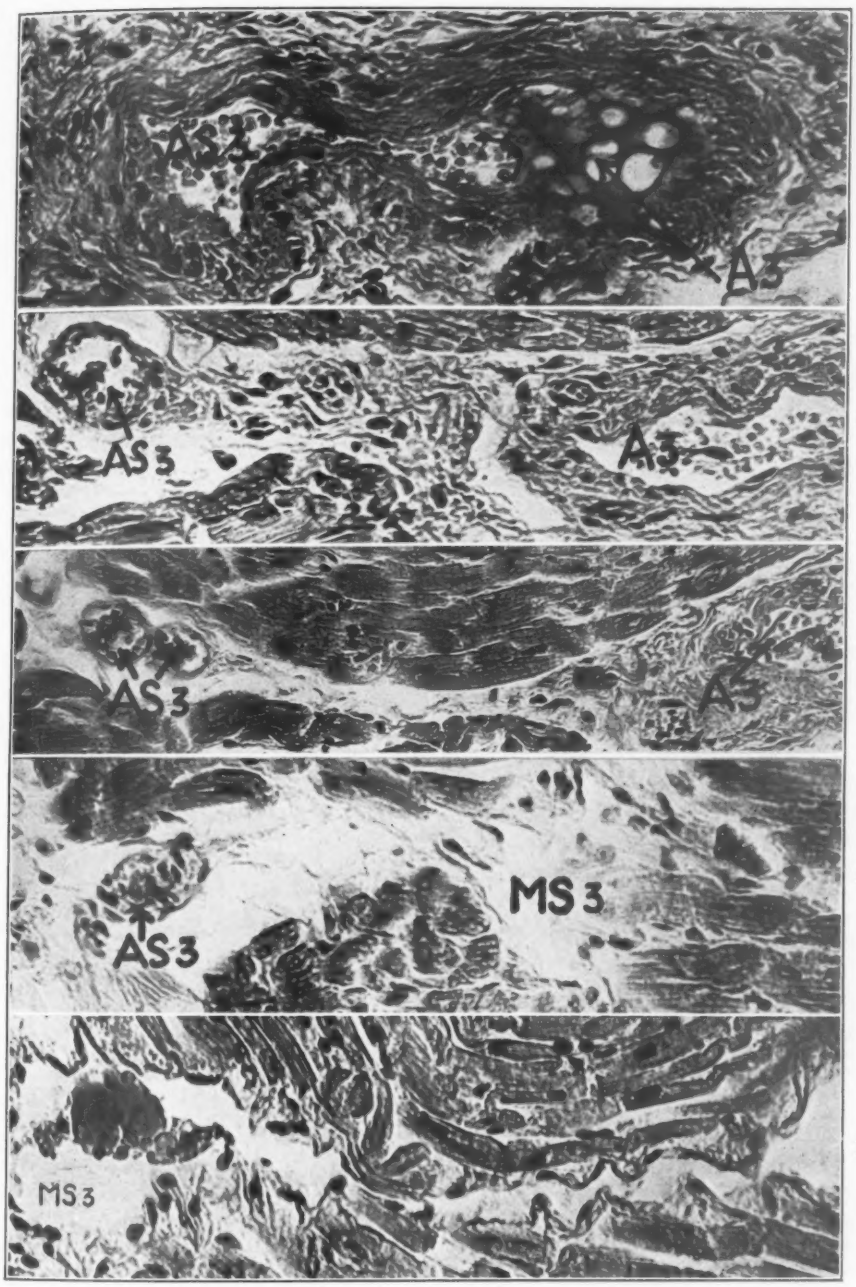

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 5.

Plate V.

Several successive stages of an "arterio-sinusoidal" vessel (AS_3) are shown. The change in the wall from the point at which it leaves the artery (A_3) to the loss of its wall upon becoming a "myocardial sinusoid" is illustrated.

(See opposite page for explanation of Figs. 1-5.)

VII, Figs. 2 and 3, and Plate VIII, Figs. 1, 2, 3, and 4. These vessels usually run a direct, short course from the artery to the heart cavity. Even in their relatively short course, however, some of these vessels give off branches which break up into capillaries.

The walls of these vessels are thicker than those of the "arterio-sinusoidal" vessels and they retain their thickness almost to the point of entrance of the vessels into the heart cavity. At times, however, they lose their thick walls immediately after branching from the parent artery. The actual thickness of the walls or the actual diameter of the lumina is difficult to measure, since none of these vessels was found with its lumen completely filled or distended. Several diameters of vessels in the collapsed state were measured and ranged from 0.04 mm. to 0.2 mm. The diameters of the "arterio-luminal" vessels as estimated from the celloidin cast (Plate II, Fig. 1) ranged from 0.2 mm. to 1.0 mm.

The "arterio-luminal" branches of the coronary arteries were found to communicate with the atria and ventricles. They appeared to be more numerous in the ventricles than in the atria.

In view of the fact that the large number of "arterio-sinusoidal" branches and "arterio-luminal" vessels just described were observed in one small block of myocardium, a search was started for similar vessels in other hearts which had been injected by various methods.[6] The search was soon rewarded, for in the first two hearts studied "arterio-sinusoidal" vessels were found and the "myocardial sinusoids" were easily recognized. In the third and fourth hearts studied, several "arterio-luminal" vessels were discovered (Plate VII, Figs. 2 and 3, and Plate VIII, Figs. 1, 2, 3, and 4). In five consecutive human hearts studied, therefore, "arterio-luminal" or "arterio-sinusoidal" vessels were found. Inasmuch as the "myocardial sinusoids" open into the lumen of the ventricle, it follows that in tissue from five consecutive hearts from which serial sections had been prepared direct vascular communications between the coronary arteries and the heart chambers were observed.

Recent contributions have shown that the coronary circulation is not limited to the common order of vessels—artery, capillary, and vein—but is safeguarded by other channels which offer collateral routes for the blood stream. The thebesian veins, for instance, have been shown[5, 6, 10, 16] to communicate with the cardiac veins, with the capillaries, and with

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Plate VI. Fig. 1.—Heart 23 Kb. section 139. Shows artery (A_3) from which an "arterio-sinusoidal" vessel (AS_2) has just branched. The "arterio-sinusoidal" vessel (AS_2) opens into the "myocardial sinusoid" (MS_2). (×360)

Fig. 2.—Heart 23 Kb, section 139. Shows the same "myocardial sinusoid" (MS_2) as shown in Fig. 1 as it approaches the ventricular cavity via the common opening (CO). The actual opening, while not shown in this section, is in the region labeled OMS_2. At the top of the figure can be seen a closed "myocardial sinusoid" (CMS). Note the fact that MS_2 is also closed in places. (×360)

Fig. 1.

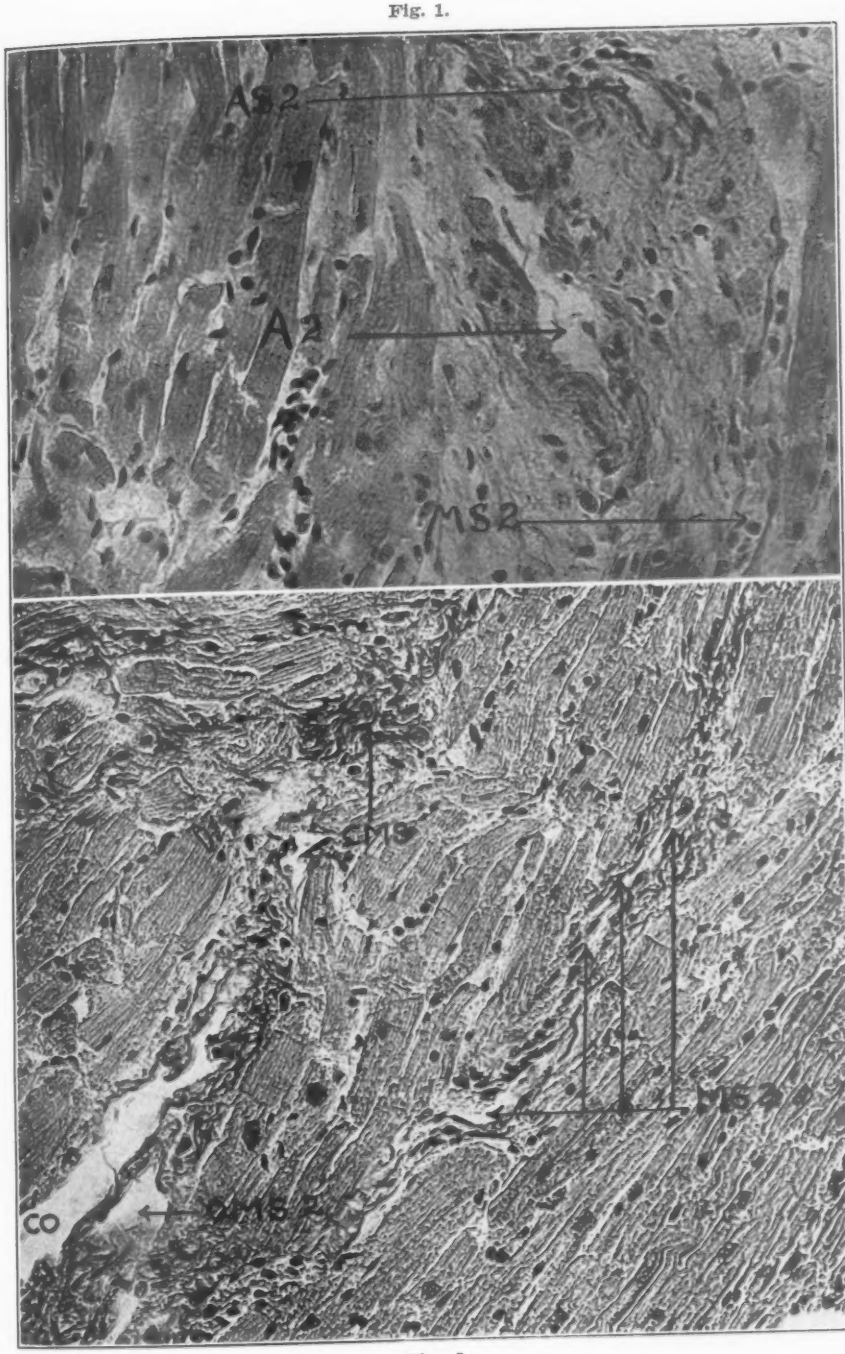


Fig. 2.

Plate VI.

(See opposite page for explanation.)

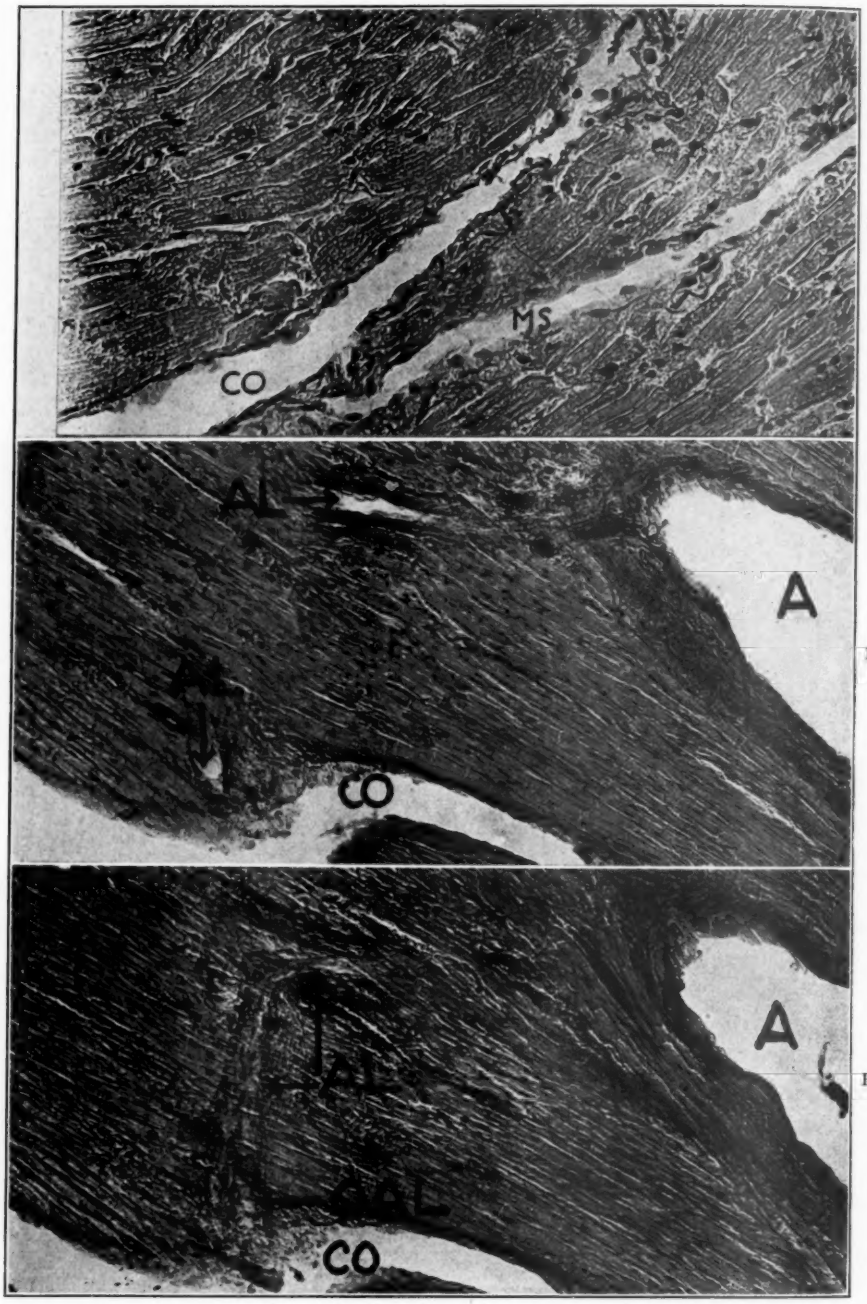


Fig. 1.

Fig. 2.

Fig. 3.

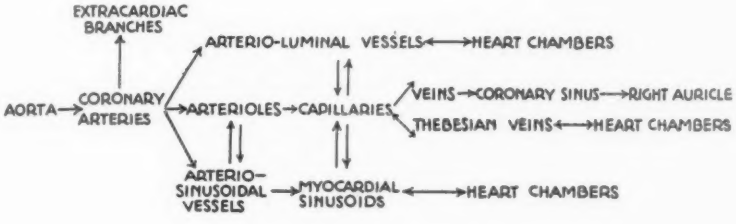
Plate VII.

Fig. 1.—Heart 23 Kb, section 142. Shows a "myocardial sinusoid" (MS) approaching the common opening (CO). (×340)

Fig. 2.—Heart 52. Shows an "arterio-luminal" vessel (AL) branching from the artery (A) and approaching the common opening (CO). Note the wall of the "arterio-luminal" vessel. (×158)

(See opposite page for further explanation of Plate VII.)

one another. More recently Hudson, Moritz, and Wearn[17] have demonstrated extensive extracardiac anastomoses of the coronary arteries which extend into the mediastinum, lungs, parietal pericardium, both surfaces of the diaphragm, and through the vasa vasorum to the abdominal aorta. The evidence presented in this paper gives additional support to the claim made by Wearn[6] in 1928; namely, that direct vascular communications other than capillaries exist between the coronary arteries and the chambers of the heart. If these various vascular channels are introduced into the scheme of the coronary circulation, it can be set up in a diagrammatic fashion as follows:



Blood entering the coronary arteries, therefore, has a possible exit through any one or all of four routes:

1. By extracardiac anastomoses;
2. By way of the capillaries and veins
   (a) into the coronary sinus or great cardiac veins and thence into the right atrium, or
   (b) through the thebesian veins into the heart chambers;
3. By way of the "arterio-luminal" vessels directly into the heart chambers; and
4. By way of the "arterio-sinusoidal" vessels through the "myocardial sinusoids" into the chambers.

The last three systems also anastomose with one another. This structural diagram is proposed in order to indicate the arrangement of the vessels and not to show the direction of the flow within them.

A somewhat similar diagram of the circulation was published by Wearn[6] in 1928, in which evidence of vascular connections between the coronary arteries and the heart chambers was presented. Inasmuch as the findings were based upon anatomical studies, no definite conclusions were drawn as to the function of the "arterio-luminal" vessels. No

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Plate VII (Continued). Fig. 3.—Heart 52. Shows the artery (A) and the "arterio-luminal" vessel (AL) which empties into the common opening (CO) at (OAL). (×158)

Figs. 2 and 3 are photographs of consecutive serial sections. A = artery. AL = "arterio-luminal" vessel. OAL = opening of "arterio-luminal" vessel into the lumen of the ventricle.

claim was made that the coronary capillaries were perfused during systole as quoted by Stella,[11] but certain speculations were indulged in which have led him to enter the field and search for the "arterio-luminal" vessels by means of a physiological method. Employing the denervated heart-lung preparation, he attempted to establish back-flow from the ventricles into the coronary arteries. Under the conditions of his experiment, the heart would beat for "one or two minutes" before beginning to fail. During these two-minute periods he was unable to establish back-flow from the chambers to the arteries and, therefore, concluded that channels between them did not exist. His results are not surprising, for it was pointed out in 1928[6] and emphasized by Leary and Wearn[18] in 1930 that, if sufficient time were allowed, the thebesian—and this should now include the "arterio-sinusoidal" vessels and the "myocardial sinusoids"—could substitute for the coronary arteries in supplying blood to the myocardium. Stella's failure to reverse the normal direction of flow and establish a back-flow in a failing heart within two minutes seems to us to have little, if any, bearing upon the existence of vascular channels between the coronary arteries and the heart chambers. Such negative evidence certainly cannot be admitted as proof that such channels do not exist.

The failure of Grant and Viko[10] to find communicating vessels between the arteries and the heart chambers led them to deny their existence. The methods employed by these workers were probably to blame for their failure. The common openings, into which the "arterio-luminal" vessels and "myocardial sinusoids" open, frequently communicate freely with the intertrabecular spaces, and this fact alone would render injection from the endocardial end almost impossible. Moreover, the openings of the "arterio-luminal" vessels usually lie deeply concealed in the intertrabecular spaces, and it is possible that Grant and Viko injected only the thebesian veins and did not find any of the "arterio-luminal" openings.

In our hands, many failures were experienced at first in attempting to inject the communicating vessels with celloidin and gelatin. The celloidin frequently solidified upon coming into contact with fluid in the arteries. The failure with the gelatin injections could be traced usually to improper temperature regulation. Careful control of these factors led to the successful injections.

Plate VIII. Fig. 1.—Heart 9B. Injection mass India ink. At the right of the figure is an artery (A) of which the "arterio-luminal" vessel (AL) is a branch. At the extreme upper left of the figure may be seen the common opening (CO). (×64)

Fig. 2.—Heart 9B. Shows a higher magnification of the "arterio-luminal" vessel (AL) and the common opening (CO) shown at the left of Fig. 1.

Figs. 2, 3, and 4 are consecutive serial sections, showing the "arterio-luminal" vessel (AL) as it approaches the common opening (CO) and then enters it at (OAL) in Fig. 4. Each figure (×247).

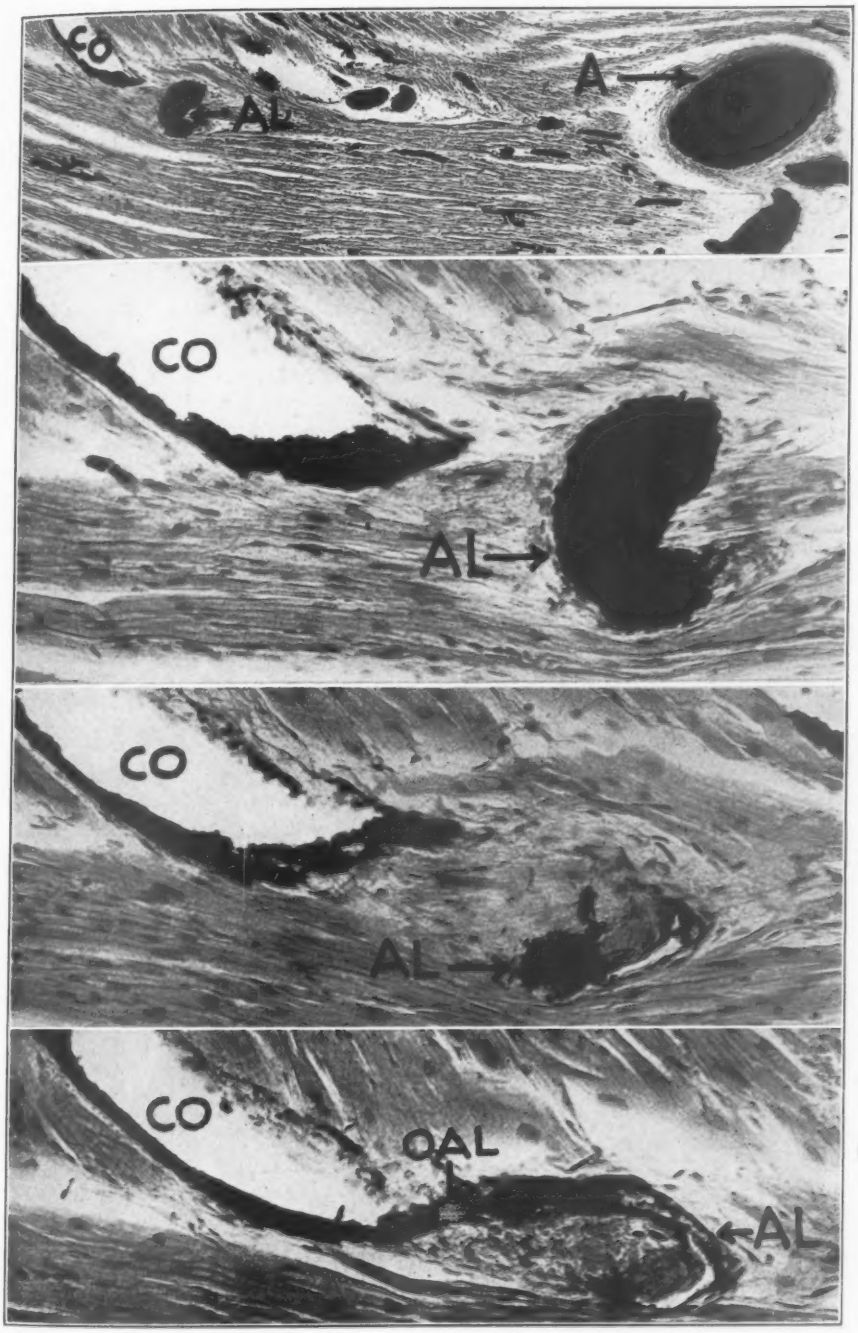

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4

Plate VIII.

(See opposite page for explanation of Plate VIII.)

SUMMARY

By the employment of injection methods, it has been possible to demonstrate vascular communications between the coronary arteries and the chambers of the heart. Serial sections and wax-plate reconstructions of these communicating vessels revealed two types which have not been described previously. The first of these communicating vessels are small branches of arteries or arterioles lying near the endocardium. They run a short course and empty directly into the lumen of the heart and, for this reason, they have been referred to as "arterio-luminal" vessels. The second type of vessel arises as a branch of an artery or arteriole and soon breaks up into sinusoids which lie between the muscle bundles and at times between the individual muscle fibers. These vessels have been referred to as "arterio-sinusoidal" vessels, and the sinusoids have been designated as "myocardial sinusoids."

The histological structure of the "myocardial sinusoids" would indicate that they play a rôle in the nourishment of the heart muscle.

It is a pleasure to express our thanks to Dr. Alan R. Moritz for his most valuable assistance in taking the photomicrographs and also for his helpful criticisms.

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THE ARTERIAL BLOOD VASCULAR DISTRIBUTION TO THE LEFT AND RIGHT VENTRICLES OF THE HUMAN HEART*

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IN ORDER to obtain a measure of the actual blood supply to a given mass of myocardium it would be necessary to know, among other things, the exact volume of muscle supplied, the distribution of the capillaries throughout the myocardial mass, the cross-section of the capillary bed (from which the capillary surface area could be determined), the velocity of blood flow through the capillaries and the tension within them. Certainly, no accurate comparison can be made of the nutrition to the two ventricles without a knowledge of the factors mentioned above.

On the other hand, it is not unfair to assume that, other factors being equal, a knowledge of the extent of the capillary bed throws some light on the blood nourishment to a given organ and, therefore, that purely anatomical studies along these lines are not without their interest and value. In the work which we are about to report it should be clearly understood that the term "blood supply" is used in this limited anatomical sense.

It is definitely pertinent to our discussion to mention that the data obtained on this question by the employment of a given technic can never be more accurate than the method itself. Here lies the crux of most of the discussion on the blood supply to the heart, anatomically considered. Up to the present, such studies have been made largely on specimens injected through the coronary arteries. Since it is vital to a critical evaluation of the results obtained from these injected specimens that only the arterial side of the vascular tree be filled, the injection mass used must be of such consistency that it will not pass beyond the capillaries into the venous system. For these purposes either a suspension of gross particulate matter (starch, barium, etc.) or a highly viscous solution (collodion, glue, etc.) is generally employed. These substances never give a complete injection of the capillaries. As a general rule and under the best of conditions one contents oneself with a uniform and even injection of vessels down to the size of arterioles. There can be little doubt that the extent and distribution of these small vessels bear a definite ratio to the ultimate capillary bed. Therefore, in discussing the "blood supply" to the ventricles, the term is limited not only to its anatomical aspects, but

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to the information on the capillary bed which can be gleaned from a study of the smaller vessels leading to the capillary distribution. Furthermore, in all probability, the further one follows the arterial tree into its ultimate ramifications, the more closely do these ramifications mirror the entire extent of the capillary bed. We have, therefore, confined our attention to this aspect of the problem.

In choosing the method of injection which is likely to give us the most accurate results, the following factors must be borne in mind:

1. The mechanical factors entering into the injection (temperature, pressure, viscosity, humidity) must be standardized and easily reproducible. This is most important. Variations in technic from specimen to specimen are bound to produce technical artefacts, making comparisons of little value.

2. The mechanical factors must not be such as grossly to distort the organ. Thus, injections with metals or other materials requiring relatively high temperatures tend to shrink the tissues by their cauterizing effect. Injection of highly viscous substances such as collodion, requires very high pressure and a long period of injection, both of which factors are inimical to obtaining an accurate picture of the delicate vascular tree.

3. The injection must be completed in a relatively short time so that the specimen may be fixed and rendered fit for microscopic examination. This examination is most important in order to rule out pathological changes such as, for example, hypertrophy, which are accompanied by corresponding changes in the vascular bed.

4. If the mass is injected through the arterial system (coronary arteries), it should not penetrate into the venous channels. As mentioned before, this is necessary in order not to confuse the arterial and venous beds.

5. The preparation should neither be fragile nor permit of appreciable distortion.

In reviewing the numerous injection methods available it seemed to us that the one least open to criticism was that employed by Gross.[1, 2] This consists of the injection of a standardized barium sulphate gelatin suspension through the coronary arteries of hearts in which rigor is allowed to pass off. The injection is carried out in a special apparatus which permits of accurate control and standardization of all the mechanical factors. Furthermore, the injection takes approximately one-half hour to complete so that the organ can be fixed at once and rendered suitable for dissection, roentgenological examination, clearing, histological study, etc.

Employing this method in 100 hearts, Gross pointed out in 1921 that the blood supply to the two ventricles was equal at birth and that from then on the left side became relatively richer in its vascular bed as compared to the right. In attempting to arrive at an explanation

for this phenomenon, there was quoted the table of weights of human ventricles compiled by Müller[3] on a material of 1,481 hearts. Since there has been some question by Whitten[4] as to the interpretation of this table, a chart made from it is again reproduced in this report (Chart 1). This chart represents the growth in weight of the left and right ventricles computed from the mean weights of the isolated ventricles in males and females. A glance at this chart shows quite definitely the sharp increase in left ventricular preponderance up to the fourth decade and gradual but slower increase thereafter.

In examining the stereoscopic roentgenograms and cleared specimens it seemed to Gross that this preponderance of left ventricular

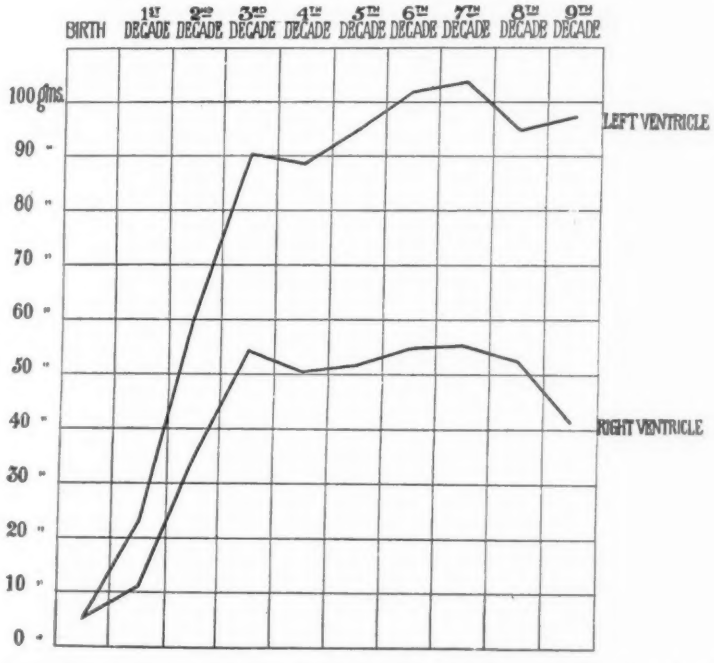

Chart 1.—Graph showing the absolute increasing weight of the right and left ventricles as age advances, and also the relative increasing preponderance of left over right side.

vascular bed over right was even greater than could be accounted for by the change in the proportion of the myocardial masses. He suggested that the right ventricle apparently lagged behind the left in the evolution of its vascular tree.

A complete confirmation of these findings soon followed in the detailed report by Campbell.[5] In 1930, however, reports appeared by Whitten[4, 6] in which, by the use of a collodion-corrosion injection technic, conclusions were arrived at which were in some respects in sharp contradiction to those of Gross. Without stating the number of hearts

*Seven are quoted of which two were from fetuses.

examined by his method* (a most important factor in the evaluation of statistical material) Whitten claimed that while the blood supply to the right ventricle was at birth at least as great as that to the left, it soon fell behind the latter in development. A gradual increasing vascular preponderance occurred on the left side which, however, reached its maximum at about the tenth year. From then on no changes took place.

A more serious objection to Gross' conclusions has been raised recently by Ehrich, de la Chapelle and Cohn.[7] These investigators pointed out the difficulties in interpreting the extent of the injected vascular beds when the heart as a whole is examined roentgenographically, since, as they stated, "it was difficult to estimate and to allow for the increase in density of the left ventricle. The difference is obvious enough when the anterior and posterior walls alone are concerned, but becomes greater in the case of the two lateral walls, through which the rays pass in a direction roughly parallel to an anteroposterior tangent. Clearly, the greater the volume of muscle through which the rays pass, the greater will be the number of vessels photographed. The appearance of relative changes in one ventricle—the right, for example—may, quite aside from the facts, depend upon matters of technical procedure." This objection is valid only to the extent that accurate and fine quantitative comparisons cannot be made by this method. Stereoscopic pictures such as employed by Gross, however, permit of sufficient comparison to determine coarse changes such as he described.

In an attempt to obtain more accurate data, Ehrich, de la Chapelle and Cohn injected fifty-one hearts (forty-one of which were normal) by the method described by Gross. The hearts were fixed in formalin, roentgenographed and cleared. Microscopic sections were taken from the left and right coronary arteries as well as from the left circumflex vessels. These investigators attempted to arrive at an estimate of the distribution of blood to the two ventricles by comparing the number and diameters of the "small branches" on the surface of the cleared hearts. "Small branches" according to them included "all branches larger than a certain size." More precisely, the term referred to all branches of the rami which are macroscopically "just visible." In order to arrive at the total diameter, the authors assumed that all the "just visible" vessels on the surface of the two ventricles must be of the same size. The question as to the accuracy of this and other assumptions made by them will be discussed further.

Dividing thirty-five of their fifty-one hearts into nine groups, these authors observed that the "small branches" increase continuously from birth to the seventh decade, the increase in the left ventricle during this period being 100 per cent and that in the right ventricle 50 per cent. Calculating this increase in terms of per unit mass, however.

they arrived at the conclusion that the developing vasculature was proportionate to the growth of the two ventricles and that there was accordingly no developing relative right-sided anemia as indicated by Gross.

With the above mentioned criticisms in mind, we decided to re-investigate the question by a method which would eliminate, as far as possible, the objectionable features discussed by Ehrich, de la Chapelle and Cohn. For the reasons already given, it was decided to inject one hundred hearts by the method of Gross. A special effort was made to select specimens which could safely be considered normal. If the clinical history, gross inspection or microscopic examination of the heart indicated a pathological condition, past or present, it was at once discarded.

The essential modification introduced into these studies was to slice the hearts transversely into strips of equal thickness so that a direct comparison could be made of the vasculature within the left and right ventricles, thus comparing unit areas of equal thickness.*

Fig. 1.—Transverse section through the ventricles of an eleven-day-old male infant. (Photograph of roentgenogram from injected specimen.)

TECHNIC

Immediately after injection, the hearts were fixed in 10 per cent neutral formalin saline.† After fixation the hearts were cut into transverse slices, 7 mm. in thickness. This was accomplished by means of a specially devised apparatus which consists of a modified meat slicer. Roentgenograms were taken of the slices according to the following technic: the exposure was three seconds at 30 inches distance, using 88 killivolts peak and 10 milliamperes. The slices were subsequently cleared by the method described by Gross, and sections were taken for histological examination. Large transverse sections, 150 mu in thickness were also cut from a number of hearts by the Christeller frozen section method. For purposes of comparison it will suffice to consider the transverse slices cut approximately one-third of the way down from the auriculoventricular sulcus to the apex. The other sections gave results similar to those to be described.

EXPERIMENTAL

Fig. 1‡ represents the roentgenogram of such a section cut from the heart of an eleven-day-old infant. The arterial vascular preponderance in the right ventricle

*Previous attempts by Gross and Antopol to estimate the ratio of injection mass per gram of myocardium by quantitatively recovering the barium sulphate used in the injection showed a large error due to ultrafiltration effect.

†Solution of formaldehyde, U. S. P., 10 parts; 1 per cent sodium chloride solution, 90 parts. This solution is rendered neutral with a weak alkali.

‡In these photographs of roentgenograms the left ventricle is to the left, the right ventricle to the right and the top of the illustration is the anterior surface of the heart.

is quite obvious. It is interesting to note, too, that even at this early age period the part of the septum which belongs to the right ventricle receives larger blood vessels and more of them than does the corresponding part of the left ventricle.

Fig. 2 is a cross-section from the heart of a three-weeks-old infant. Here again the right ventricular arterial vascular preponderance is very definite. Not only are the vessels more numerous in the right ventricle and in the right ventricular portion of the septum but their lumina are distinctly larger. It is to be noted that the type of vascular distribution is the same in both ventricles, namely, the superficial

Fig. 2.

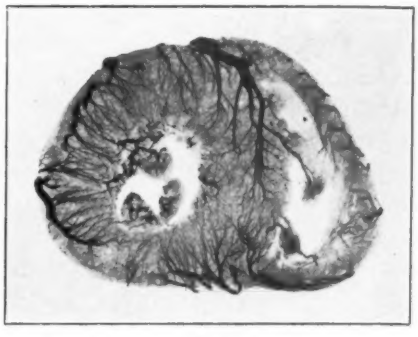

Fig. 3.

Fig. 2.—Transverse section through the ventricles of a three-week-old male infant. (Photograph of roentgenogram from injected specimen.)

Fig. 3.—Transverse section through the ventricles of a five-month-old male infant. (Photograph of roentgenogram from injected specimen.)

Fig. 4.—Transverse section through the ventricles of a four-year-old male child. (Photograph of roentgenogram from injected specimen.)

vessels rapidly dichotomize and form a series of broomlike structures which penetrate through the ventricular wall at right angles to the surface, reaching almost to the endocardium.

At the fifth month of life (Fig. 3) the myocardial preponderance of the left ventricle over the right is definitely established. Nevertheless, it will be noticed that for a given area of myocardium the amount of fair-sized and fine vessels is approximately the same in both right and left ventricles.

The same statement may be made of the four-year-old infant's heart represented in Fig. 4. Particular attention should be paid to the fact that both the left and right ventricular portions of the interventricular septum are equally richly supplied with fine blood vessels.

The same description also holds true for the nine-year-old heart pictured in Fig. 5. Here the broomlike arrangement of the myocardial trees is beautifully represented. Since the right ventricle is conspicuously thinner than the left, it will be observed that the myocardial vascular brooms take on a slanting arrangement in the former. Whitten has called attention to this and believes that it has some significance in reference to the lesser frequency of arteriosclerosis in the right cor-

Fig. 5.—Transverse section through the ventricles of a nine-year-old male child (Photograph of roentgenogram from injected specimen)

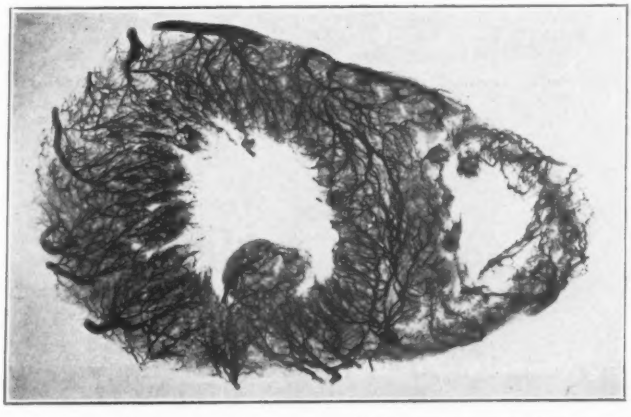

Fig. 6.—Transverse section through the ventricles of an eighteen-year-old male. (Photograph of roentgenogram from injected specimen)

onary branches as compared to those of the left. This question will be discussed subsequently. At this age period the proportion of small and large blood vessels to left and right ventricles is still approximately equal.

In Fig. 6, a cross-section of the myocardium of an eighteen-year-old boy, several differences are becoming discernible. By close inspection it can already be observed that, per unit area of myocardium, the left ventricle is somewhat richer in blood vessels. This is particularly well brought out in the interventricular septum. Another important factor which can be noted is that the septal anastomoses are becoming somewhat more conspicuous (better seen on stereoscopic examination).

By the age of twenty-nine years (Fig. 7) it becomes quite clear that the left ventricular myocardium is richer in blood supply than the right. Inspection of the myocardium of the two ventricles and particularly of the septum shows this quite distinctly.

Fig. 8 (heart of thirty-seven-year-old patient) shows very beautifully the intensely rich blood supply of the left ventricle and the definitely lesser blood supply of the right ventricle. The fact that we are here examining similar thicknesses of

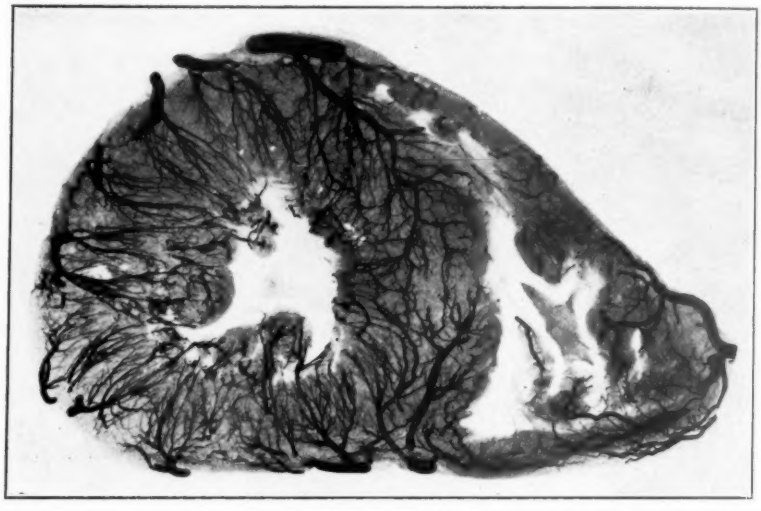

Fig. 7.—Transverse section through the ventricles of a twenty-nine-year-old male. (Photograph of roentgenogram from injected specimen.)

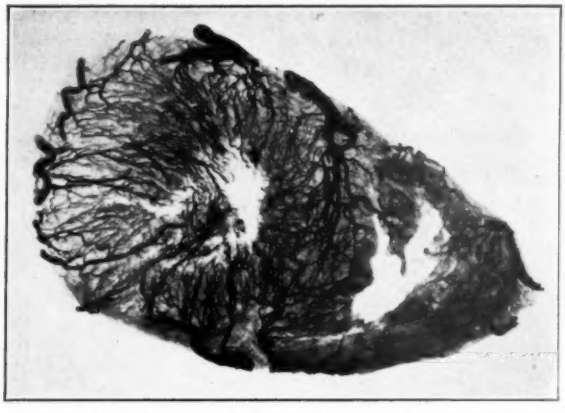

Fig. 8.—Transverse section through the ventricles of a thirty-seven-year-old female. (Photograph of roentgenogram from injected specimen.)

specimens may bear repetition. Note the distinctly richer blood supply of the left ventricular portion of the septum as compared to the right and the very markedly increased septal anastomotic vessels. This well-established left ventricular arterial preponderance is now carried on consistently.

Fig. 9, which represents the heart of a forty-three-year-old person, shows the rich left ventricular supply, the exceedingly rich blood supply to the papillary muscles of the left ventricle, the considerably lesser distribution of vessels in the right

ventricle and in the right ventricular septum. The septal anastomoses are very distinct. It is to be noted in this illustration that because of the slightly greater thickness of the right ventricle, the broomlike structure of the arterial dichotomy reappears.

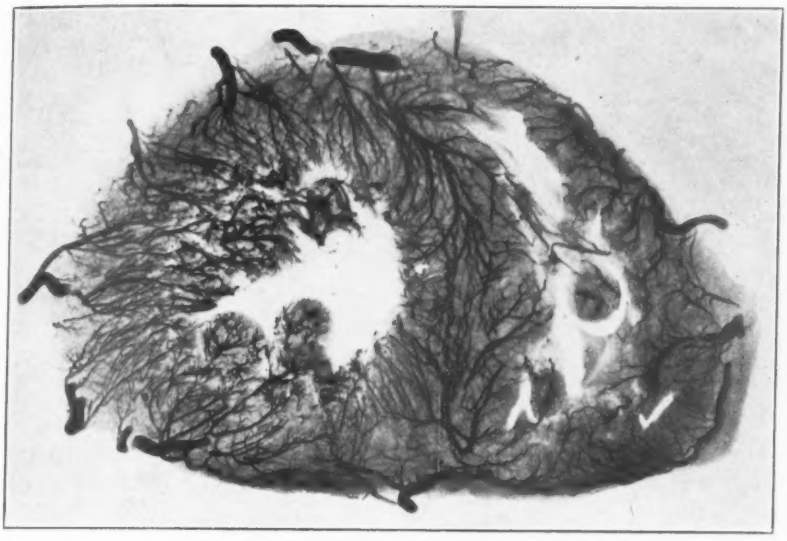

Fig. 9.—Transverse section through the ventricles of a forty-three-year-old male. (Photograph of roentgenogram from injected specimen.)

Fig. 10.—Transverse section through the ventricles of a forty-five-year-old male. (Photograph of roentgenogram from injected specimen.)

Fig. 10 (patient forty-five years old) again shows the definite left ventricular arterial preponderance and the consistently richer septal anastomoses. Here the right ventricular wall is somewhat thinner with some loss in the regularity of the broomlike arterial dichotomy.

Increasing age periods now show as the most conspicuous changes an even wider and richer septal anastomosis with persisting and increasing left ventricular vascular preponderance. This is seen in Fig. 11, which represents a cross-section of the heart of a sixty-year-old person.

Fig. 12 is a cross-section of the heart (patient thirty-two years old) taken from a specimen which shows an unusually beautiful injection. This was probably due

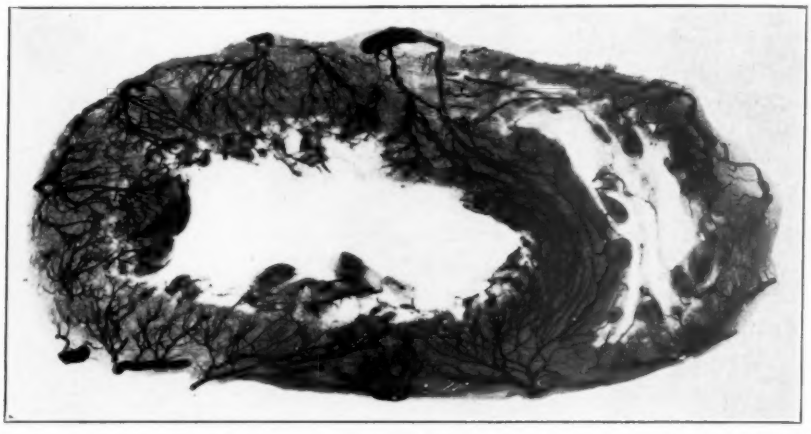

Fig. 11.—Transverse section through the ventricles of a sixty-year-old female. (Photograph of roentgenogram from injected specimen.)

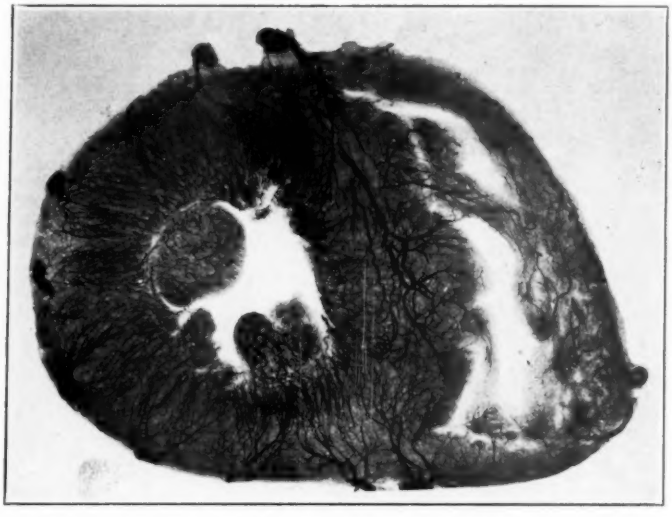

Fig. 12.—Transverse section through the ventricles of a thirty-two-year-old male. (Photograph of roentgenogram from injected specimen.)

to the fact that the heart was injected for a somewhat longer period of time and was completely flaccid before the injection. The striking difference in vascularity as between the left ventricle and the right leaves no question whatsoever with regard to the left ventricular vascular preponderance at this age period. One could not, of course, count these vessels since they are so numerous, but a simple inspection is quite sufficient to make this point clear. In particular, there is to be noted the amazing difference between the fine vascular distribution in the left ventricular

septum as compared with that of the right. Because of the excellence of the injection of this specimen, Christeller frozen sections were studied under the binocular microscope. It was at once evident that it would be highly inaccurate to attempt to count the finest vessels in the myocardium. Here, however, a simple examination again amply confirmed the observations made by the examination of roentgenograms and cleared specimens.

Although only twelve illustrations are submitted in this article, it may be stated at once that in our observation of the hundred cases which form the material of this paper, the rather abrupt shifting of vascular preponderance from the right side to a state of where both sides are about equally supplied, occurred relatively early in life (within the first few months). Then came a period of approximately one decade when it was somewhat difficult to decide which side of the heart contained more blood vessels per unit volume. From the first decade on, however, the increase in left ventricular vascular preponderance was consistent and gradual, and with it came the widening of the septal anastomotic channels (better seen in stereoscopic examination and in the cleared specimens).

A study of all the preparations leaves two very definite impressions in mind: the eventual development of left ventricular vascular preponderance and the increase in septal anastomoses seen particularly well after the third decade and increasing consistently with age.

DISCUSSION

A discussion of the above mentioned findings must concern itself largely with the reasons for the discrepancies between our conclusions and those of Whitten and of Ehrich, de la Chapelle and Cohn. With regard to Whitten, it may be said that undoubtedly the paucity of his material together with the unusually unsuitable technic employed by him may have been responsible. It is to be remembered that the technic used by Whitten (collodion-corrosion method) requires several days for completion, does not render the heart suitable for microscopic examination, requires enormously high pressures which may possibly distort the preparation and has a tendency to leak from the arterial to the venous side. A brief reference to our earlier discussion on the criteria of adequate injection technic will show at once that Whitten's technic leaves much to be desired.

It has already been mentioned that Whitten questioned Gross' conclusions that Müller's tables of weights furnished evidence of a consistently increasing left ventricular myocardial preponderance from birth to the ninth decade. In substantiation of his contention Whitten also quoted a table of weights from Müller's monograph. The difference here is obviously due to the fact that Whitten's criticism is based on a table presenting entirely different data; indeed, data which include the very questionable and arbitrary division of the septum into its proportions as to the left and right ventricles. The table quoted by Gross deals only with the isolated ventricles exclusive of the septal portions.

The discrepancy in the findings of Ehrich, de la Chapelle and Cohn can be accounted for in several ways. First, these authors assume

that a "small branch" (superficial) conveys the actual supply to what may be regarded as a unit territory. In calculating their results, however, they also tacitly assume that "unit territory" is equivalent to unit mass of myocardium. This is exactly where the difference lies as between their conclusions and our observed results. The territory supplied by a "small branch" in the left ventricle is considerably smaller than that supplied by a "small branch" in right ventricle as our illustrations clearly show. These authors find that the number of "small branches *of* the left ventricle (superficial) increases during the period of life about twice as much as the right one." Since, however, the left ventricle during this period enlarged about twice as much as the right, they conclude that the blood supply of the two ventricles increases with increasing years in direct proportion to weight. However, when these authors use the term "small branches *of* the left ventricle," they really refer to "small branches *on the surface of* the left ventricle." Obviously, the very increase in thickness of the left ventricle carries with it at least a proportionate increase in "small branches *of* the ventricle." This has not been taken into account by Ehrich, de la Chapelle and Cohn. Furthermore, their counts were made on thirty-five hearts, a number in our opinion too few for such detailed analysis. An attempt made by us to count these superficial vessels was rather unsuccessful. We found it extraordinarily difficult to determine what vessels should be considered as "just visible" and what not. An examination of their own Curve 2 (p. 263 of their article)[7] discloses not inconsiderable variations in their figures. Moreover, the correctness of the assumption by these authors that the diameters of the counted "small vessels" on the surface of both ventricles are the same has by no means been substantiated. On the whole it seems to us that the method used by them is subject to far more inaccuracies than even the first method used by Gross, viz., direct inspection of the stereoscopic roentgenograms.

We do not wish to enter into a discussion at this time of the possible physiological significance of this gradually developing left ventricular vascular preponderance. Experiments are under way to investigate this point. The importance of the gradually developing septal anastomoses with age has already been emphasized by Gross, who suggested that this may serve as a compensatory factor during the later age periods when sclerotic changes begin to appear particularly in the branches of the left coronary artery. Histological examination of the age period changes in the coronary arteries to be published shortly by Gross, Kugel and Epstein shows that with advancing life there is a gradual fibro-elastification of the smaller myocardial vessels, particularly in the left ventricle, with some disappearance of smooth muscle elements. These vessels are consequently rendered relatively passive to vasomotor impulses. Whether the septal anastomotic in-

crease is a compensatory process as a response to these regressive changes in the left ventricular myocardial blood vessels can only be surmised. In a later publication, it will be shown that these septal anastomotic vessels play an extraordinarily important rôle in coronary artery disease in which myocardial infarction takes place.

CONCLUSION

By means of a new technic whereby it is possible to study the vascular distribution in the myocardium and to compare unit areas in the left and right ventricle, it has been definitely demonstrated that early in life there is a right ventricular vascular predominance, that there soon follows an equalization of the vascular supply which lasts for approximately one decade and that thereafter the left ventricular myocardium assumes an increasing preponderance in its vascular bed over that of the right.

It has also been shown that, particularly after the third decade in life, the septal anastomoses increase very conspicuously in their extent.

Both of these observations confirm the earlier report by Gross in this field.

An explanation is suggested for the reported differences from these conclusions.

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CARDIAC HYPERTROPHY OF UNKNOWN ETIOLOGY IN YOUNG ADULTS

A Clinical and Pathological Study of Three Cases*

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IN THE course of two and a half years, there have been observed three young men who presented an unfamiliar picture. Clinically, the outstanding feature was a considerable degree of cardiac enlargement, for which no cause was apparent. All died within a year after the symptoms became well established. The lesions in the three hearts, as studied at autopsy, though exhibiting many points of similarity, were not identical. The etiology remained obscure.

CASE REPORTS

Case 1.—Unit No. 69800. S. R., white male, aged twenty-nine years, automobile mechanic, married, was first admitted to the hospital on September 17, complaining of palpitation which had been present continuously for two and one-half months. His father died at the age of fifty-six, of heart disease. He had been unusually healthy. Tonsillectomy was performed at the age of eleven. He had gonorrhea at twenty, but denied syphilis. At the age of twenty-four, he was in South America for a short period, while in the Navy. He had been married for six years. His wife and two children were living and healthy; there had been no miscarriages. His consumption of alcohol and tobacco was very moderate. For twelve years, he had been an automobile mechanic. His usual weight ranged from 190 to 210 pounds.

He first was conscious of irregularity of the heart five years previously while working in South America. After a day's labor, during which he was much exposed to sun and fumes, he would lie down to rest. It was then that he became aware of the irregular and rapid beating of his heart, which occurred in paroxysms lasting from five to fifteen minutes. The attacks increased in frequency until he had several each day. After his return to New York they became less frequent, recurring at irregular intervals. For two and one-half months, however, tachycardia had persisted almost continuously and he had felt weak. He consulted several physicians without relief. He was unable to obtain the proper amount of sleep because of the pounding of his heart and throbbing of his arteries.

Examination showed a large, well-developed man, who appeared to be quite ill. There was no dyspnea or cyanosis. The tonsils had been well removed. The thyroid was not palpable. The lungs were clear. The heart was considerably enlarged, dullness extending 13 cm. to the left in the fifth space, and 4 cm. to the right in the fourth space. The rate was variable, at times 120 to 160, with regular rhythm, then a few irregular beats, followed by a sudden drop to 60. The sounds

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were of moderate intensity. There was splitting of the first sound at the apex. No murmurs were heard. The peripheral vessels were not thickened. The blood pressure was 110/80 mm. The liver was not enlarged. There was no clubbing of the fingers. No edema was present.

The temperature was normal and remained so throughout his stay in the hospital. The blood count showed: R.B.C. 6,000,000; hemoglobin (Dare) 95 per cent; leucocytes 12,000, with 63 per cent polymorphonuclears. The Wassermann reaction of the blood was negative. The urine contained a very faint trace of albumin, but no casts or red blood cells. X-ray films of the teeth did not show any root abscesses.

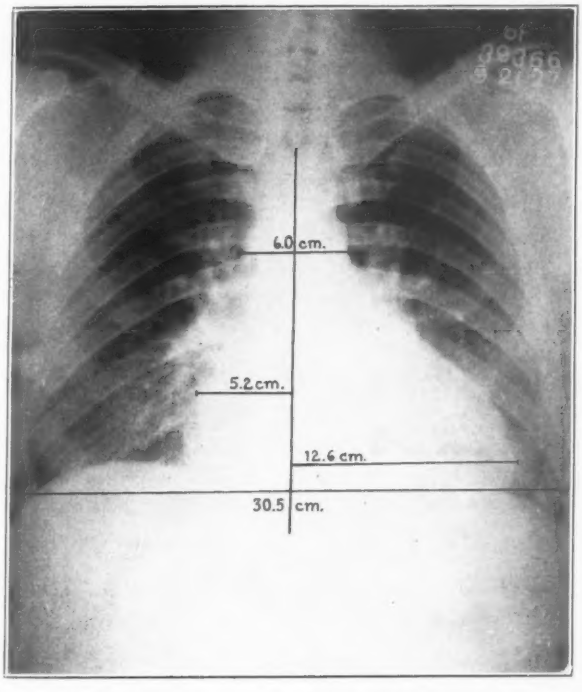

Fig. 1.—(Case 1) Teleroentgenogram of the heart, taken four days after the patient's first admission to the hospital. The enlargement is chiefly to the left.

A teleroentgenogram of the heart showed the transverse diameter to be increased, but the aorta was not widened. The total transverse diameter measured 17.8 cm., the great vessels 6.0 cm., and the internal diameter of the chest 30.5 cm. (Fig. 1).

The heart rate varied greatly from day to day and from hour to hour. Electrocardiograms were made daily and often, several times in the course of twenty-four hours. The dominant rhythm was a tachycardia having its origin in the junctional tissues, with rate of 50 to 160. Numerous ventricular premature beats, arising both in right and left ventricles, occurred. On a number of occasions transitions were photographed, showing changes in rate and in the origin of the pacemaker (Fig. 2, *A*). The P-R interval, when it could be measured, varied from 0.22 to 0.31 second, and there was widening of QRS when nodal rhythm, with slow rate, was present. The T-wave was at first inverted in Lead I and upright in Leads II and III, but later, following administration of digitalis, T_2 and T_3 also became inverted.

Administration of quinidine, by mouth, in moderately large doses, did not affect either the rate or the rhythm. The use of digitalis, first in full doses, and then in maintenance ration, slowed the rate to 60, with occasional short paroxysms of tachycardia to 120. The blood pressure rose to 130/70. On discharge, after four weeks in the hospital, the patient felt greatly improved, and was instructed to continue with small daily doses of digitalis.

He did not return to the out-patient department for further observation and was lost sight of until June 4 of the following year (eight months later), when he came

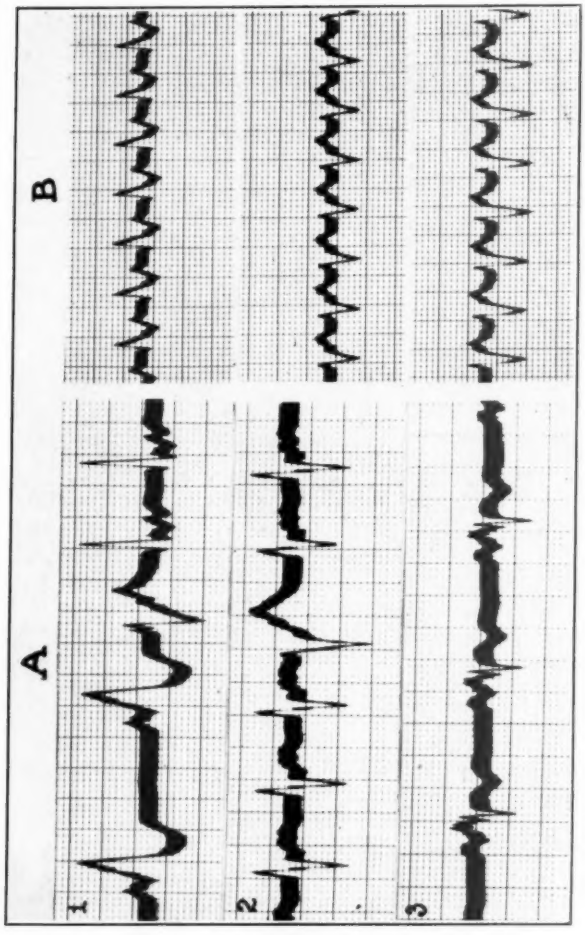

Fig. 2.—(Case 1) *A*. September 21, four days after the first admission to the hospital. In Lead I is shown the transition from a rhythm initiated in the upper portion of the junctional tissues, with rate of 50 and aberrant ventricular complexes, to one originating lower in the A-V bundle, with rate of 120 and normal intraventricular conduction time. The shift in the location of the pacemaker is ushered in by a premature beat arising in the ventricle. In Lead II, A-V nodal rhythm continues, as at the end of Lead I. In Lead III, the impulse again has its origin in the upper part of the node, the rate being 64. The QRS interval is again widened.
B. June 7 of the following year (three days before death). Auricular tachycardia; rate 170. P-R (conduction) time is 0.19 second. There has been a marked change in the form of the complexes.

to the clinic desperately ill. He stated that after leaving the hospital he again went to South America on a job, but had to leave after five weeks, because of recurrence of the paroxysms of tachycardia. He returned to this country two weeks ago, and since that time had great difficulty in getting his breath. He had taken digitalis in liquid form, without benefit.

On admission, he was cold and a clammy sweat covered the skin. The respirations were rapid and shallow. The pulse was barely palpable. The heart rate was about 180, and the rhythm apparently regular. The temperature was 99.4° F. The blood pressure was 134/90. The blood Wassermann reaction was again nega-

tive. A blood culture showed no growth. The leucocyte count was 13,000, with 42 per cent polymorphonuclears. There was no anemia. The blood urea was 41 mg. per 100 c.c. Electrocardiograms showed at times auricular tachycardia, with rate of 170 and incomplete bundle-branch block; and at other times A-V nodal rhythm with rate of 70 to 80, with complete bundle-branch block, and numerous ventricular premature beats. When the rate was slow, QRS measured 0.17 second, R was notched and T was inverted in all leads. The records were very different in form from those previously obtained. (Fig. 2, *B.*)

Dyspnea persisted and was more marked during the paroxysms of tachycardia. Administration of large doses of digitalis was without apparent benefit. He began spitting up blood, evidently as a result of pulmonary infarction. The temperature rose to 103.4° F., and the leucocyte count to 31,000, with 79 per cent polymorphonuclears. Orthopnea and prostration became extreme, and he died on June 10, six days after entering the hospital.

Autopsy No. 10017.—The autopsy was performed by Dr. L. M. Rousselot. External examination showed slight cyanosis of the face and nail-beds. There was pitting edema of the crural regions and feet.

Thoracic Cavity: The pericardial sac contained 30 c.c. of clear, straw-colored fluid. *In situ,* the heart appeared to be enormously enlarged, measuring 19 cm. in its maximum transverse diameter. The right pleural cavity contained 100 c.c. of thin, blood-tinged fluid.

Heart: The heart weighed 740 grams. There were numerous pericardial hemorrhages. A few epicardial hemorrhages were seen on the posterior surface of the right auricle, and also on its lateral surface near the base of the superior vena cava. The right auricle was covered with numerous fine, fibrous tabs. A small tendinous plaque, measuring 1 cm. in diameter, was found near the base and posterior surface of the right ventricle. All the chambers of the heart were greatly dilated. The musculi pectinati of the right auricular appendage were hypertrophied; no thrombi were present. The leaflets of the tricuspid valve were enlarged, but the cusps were not thickened and the chordae tendineae were thin and delicate. The columnae carneae and papillary muscles in the right ventricle were markedly hypertrophied. There was no scarring of the wall on the right side. The pulmonary leaflets did not present the same relative increase in size as did those of the tricuspid valve. The wall of the left auricle was moderately hypertrophied. The mitral cusps were enlarged and thickened. There was edema of the free margins, and near the line of closure of the aortic leaflet there were a number of fine granular excrescences, covering an area 0.5 cm. in diameter. A small area of atheroma was found at the base of this same leaflet. The papillary muscles, columnae carneae, and myocardial wall of the left ventricle were hypertrophied. The chordae were thin and delicate. There was gross scarring of the posterior papillary muscles of the aortic leaflet of the mitral valve. The cavity of the left ventricle, in addition to being dilated, extended well down to the apex, and here the wall of the myocardium was quite thin, measuring 0.5 cm. This was in contrast to the remainder of the wall of the ventricle, which measured 2.4 cm. in thickness. Several small thrombi filled in the recesses between the columnae carneae. Beneath the aortic ring, there was slight thickening of the septal surface of the endocardium, which at this place measured 2 mm. The aortic leaflets were increased in size, but not thickened.

The coronary arteries were not occluded at any point. In the anterior descending branch there were many fine areas of atherosclerosis without calcification.

There were multiple infarcts in the lungs, and a single infarct was present in the right kidney. There was chronic passive congestion of the lungs, liver, spleen, pancreas, and kidneys.

Microscopic Examination of the Heart.—Myocardium: A majority of the muscle fibers were hypertrophied; their striations were distinct and the nuclei were well defined. In the areas of infarction, there appeared varying stages of degeneration and repair. In places, the muscle fibers had lost their characteristic, intense staining reaction, and occasionally showed vacuolated cytoplasm, with pyknotic nuclei. Other areas of the myocardium were replaced by diffuse connective tissue scars.

Endocardium (interventricular septum): A dense layer of fibrous tissue was seen beneath the endothelium. This was infiltrated with small and large lymphocytes. In places, the endothelium was denuded, and attached to these sites were small thrombi.

Anatomical Diagnosis.—Cardiac hypertrophy and dilatation; infarcts of the heart, old and recent; fibrous thickening of the endocardium of the left ventricle; thrombi in the left ventricle; infarcts of the lungs; infarct of the right kidney; right hydrothorax; edema of the lower extremities; chronic passive congestion of the lungs, liver, spleen, pancreas, and kidneys; congenital malformation of the aorta (common origin of the innominate and left common carotid arteries); congenital malformation of the lungs (anomalous fissuration).

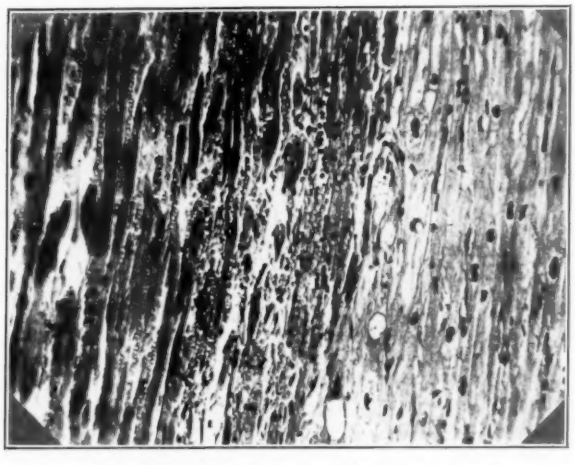

Fig. 3.—(Case 1) Section through the myocardium, showing an area of infarction of recent origin. Hematoxylin and eosin; ×160.

Final Note.—Cardiac hypertrophy and dilatation were the dominant features of the post-mortem examination. There were no inflammatory or degenerative lesions in any part of the cardiovascular system. The various embolic phenomena were secondary to the intracardiac thrombi. After careful study of all of the material, no etiological basis for the heart lesion could be found.

CASE 2.—Unit No. 73296. E. R., a white, single male, aged eighteen years, was a high school student. The patient was admitted to the hospital on August 4, complaining of rapid heart action of eight weeks' duration. The family history was entirely irrelevant. The parents were intelligent, and the young man lived in comfortable surroundings, in a private house. He had enjoyed good health. At the age of eight, he had influenza, and at fourteen, had dry pleurisy. He had had only one attack of tonsillitis, which occurred at the age of fifteen. Two and one-half years before admission (at the age of fifteen and a half years) he had an attack of palpitation, which lasted for two days and stopped after taking digitalis. No other cardiac symptoms followed this short paroxysm, and he had been remarkably well.

He lived the normal life of a high school boy, and worked during the summers. He took no tobacco or alcohol.

Eight weeks before admission to the hospital, he became aware of rapid heart action, which came on suddenly after eating ice cream. Tachycardia persisted for ten days, with rate of about 120, and stopped abruptly after taking digitalis and resting in bed. For four days, the pulse rate remained slow. During this time,

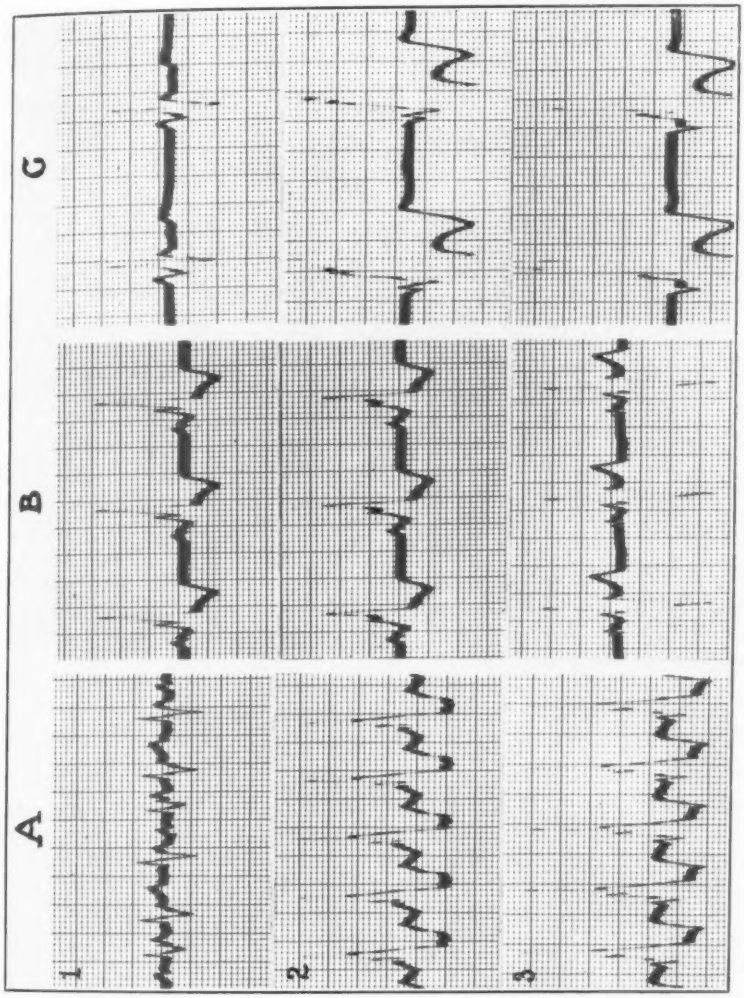

Fig. 4.—(Case 2) *A*. August 14 (first admission to the hospital). Auricular tachycardia, with rate of 140. In Lead I, occasional premature beats appear, which originate probably in the ventricle. P-R (conduction) time is 0.12 second. There is widening and deformity of the QRS group.
B. Sept. 7. Regular sinus rhythm, with rate of 74. The T-wave is inverted in Leads I and II, and there is still disturbance in intraventricular conduction.
C. Oct. 2. Junctional (A-V nodal) rhythm, with rate of 52. The pacemaker has shifted and there are striking changes in the form of the complexes. The T-wave is now partly upright in Lead I, but sharply inverted in Leads II and III.

he felt poorly, and vomited once. His physician said that he had heart-block and gave him adrenalin. At the end of this four-day period (six weeks before admission) his pulse again suddenly rose to about 120, while he was lying down after supper, and the rapid rate continued, except for occasional short intervals when his physician pushed digitalis therapy. Because of the previous occurrence of block, this drug had been used with caution. The patient had been in bed for six weeks. There was no precordial pain, dyspnea, or edema.

Examination showed a tall, poorly developed, pale, young man, breathing easily and quite comfortable. The tonsils were small and buried. There were no signs

of thyroid disturbance. The heart was enlarged, dullness extending 13 cm. to the left in the fifth space, and 5 cm. to the right in the fourth space. The rhythm was regular; the rate approximately 120 and regular. The sounds were of good quality and no murmurs were heard. There was no thickening of the peripheral vessels. The blood pressure was 130/80. The temperature was 100.2° F. Blood count showed: R.B.C. 4,070,000; hemoglobin 70 per cent; leucocytes 9,100, with 75 per cent polymorphonuclears. A Wassermann reaction of the blood was negative. The blood culture was negative. The urine showed no albumin or sugar. Under the microscope, no red blood cells were seen.

A teleroentgenogram of the chest showed the heart shadow to be enlarged in all diameters and the auricles were increased in size. There was no dilatation of the aorta. The transverse diameter of the heart measured 17 cm., the aorta 6.5 cm., and the internal diameter of the chest 26 cm.

The first two electrocardiograms showed auricular tachycardia, with rate of 145 to 160. The R-wave was notched and the T-wave inverted in all leads. Subsequent records showed considerable variability in the form of the complexes, with short runs at somewhat faster rate, due to beats originating at other foci in the ventricles or junctional tissues (Fig. 4). Digitalis and quinidine had but little effect on either the rate or rhythm. The temperature, for the most part, was normal, with occasional brief spikes to 100.4° F., or less.

On September 6 (about a month after admission) tonsillectomy was performed under local anesthesia. Microscopic examination of sections of the tonsils showed deep crypts without pus. The capsules were thickened and there was the usual infiltration with lymphocytes which is seen in chronic tonsillitis. On the morning following the operation, sinus rhythm appeared, with rate of 78. Incomplete bundle-branch block was present, with QRS of 0.13 second. The P-R interval was 0.14 second. T_1 was inverted, and T_2 and T_3 were upright. Sinus rhythm persisted for about two weeks, and subsequently A-V nodal rhythm, with bundle-branch block, was observed. T_1 became diphasic, T_2 and T_3 inverted, although no digitalis was given during this time. Salicylates were given in moderate dosage, because it was believed that the condition might be rheumatic in origin. Following operation, the temperature gradually returned to normal. The patient was discharged on October 10 (two months after admission), much improved. He had gained several pounds in weight.

He apparently got on comfortably for three months, but was readmitted on January 11 of the following year, again complaining of tachycardia. The rapid rate began three weeks previously, again following excessive indulgence in ice cream. He was put to bed and given digitalis for two weeks; he then became nauseated and vomited. The tachycardia persisted. He complained of having had several fainting spells in bed, associated with dyspnea and increase in the heart rate.

Examination on admission showed a temperature of 100° F., heart rate of 124, with regular rhythm, and blood pressure 94/70. A systolic murmur was heard at the apex, which had not been observed previously. The spleen was not palpable. The heart size was as noted at the time of the former admission. Examination of the blood showed: R.B.C. 4,560,000; hemoglobin 73 per cent; leucocytes 8,300, with 86 per cent polymorphonuclears. An electrocardiogram showed auricular tachycardia, with rate of 145. The rhythm was quite regular. The ventricular complexes were aberrant, and resembled very much the record made at the time of his first admission to the hospital. On the following evening, the temperature had risen to 101.4° F. The rhythm became irregular and somewhat slower. It was thought that auricular fibrillation was present, although no cardiogram was made. On the third day in the hospital, following an enema and while sitting on the bed-pan he gave a groan and died suddenly within a few seconds.

Autopsy No. 10125.—The autopsy, performed by Dr. W. C. von Glahn, was limited to examination of the heart and lungs. External inspection showed no edema of the feet or legs. There was intense cyanosis of the nail-beds and moderate cyanosis of the lips.

Thoracic Cavity: The pericardial sac contained only about 15 c.c. of blood-tinged fluid. The apex of the heart was against the lateral chest wall in the left midaxillary line. The transverse diameter of the heart, in situ, was 16.5 cm. Over the base of the heart, in the region of the great vessels, were fibrous adhesions.

Heart: The heart was greatly enlarged and weighed 750 grams. The apex was formed about equally by the right and left ventricles. The capillaries in the epicardium were very prominent. On the posterior surface of the left ventricle, about 1.5 cm. below the auriculoventricular groove and covering this groove, was a small, tendinous plaque. A few hemorrhages were found beneath the epicardium of the right auricle. The heart muscle was firm. The right auricle was greatly enlarged; its walls were enormously hypertrophied, measuring 11 mm. in the thickest portion. The endocardium of the auricle was thickened in places to such an extent that it was no longer possible to see the underlying myocardium. The tricuspid valve leaflets were thin and delicate. The papillary muscles and columnae carneae of the right ventricle were enormously hypertrophied, as were also the musculi pectinati of the auricle. The endocardium of this ventricle was thin and transparent, except for a few small areas near the apex, where it was grey and somewhat opaque. At the apex of the right ventricle were four slightly irregular, greyish masses, surrounded by post-mortem clot and not attached to the wall of the ventricle at any point. The largest of these was not more than 1 cm. in its greatest dimension. They were soft and lay between the hypertrophied columnae carneae. It was impossible to say from the gross appearance whether these were thrombi or represented post-mortem clot. The conus of the ventricle was greatly dilated. The pulmonary leaflets appeared normal.

The left auricle was slightly dilated; its wall measured 4 mm. at the thickest portion. In contrast to the right auricular appendage, the left auricular appendage was small and the musculi pectinati were not hypertrophied. The mitral valve was normal in appearance, except for slight marginal edema of the posterior leaflet. The chordae tendineae were thin and delicate. The papillary muscles and columnae carneae of the left ventricle were hypertrophied. The endocardium was opaque and grey in color. In the lower half of the septum the endocardium was greatly thickened, appearing as a yellowish grey layer. The myocardium in this area was not softened. The aortic leaflets were thin and delicate. In the musculature of the right auricle were numerous slightly opaque, yellowish areas, the largest of which measured 3 by 5 mm. The myocardium was of coarse texture. In the left ventricle, there was an occasional small grey area; yet everywhere throughout the heart the knife, as it cut, encountered unusual resistance, making an audible creaking noise.

In the interventricular septum, beneath the area where the endocardium was thickened, the muscle had been replaced by dense connective tissue, and near the margins of this connective tissue the muscle appeared slightly sunken and dark red, in contrast to the more greyish red muscle elsewhere. The alteration in the interventricular septum was very extensive and in one of the prominent columnae carneae, close to the posterior margin of the septum, were encountered areas which were opaque, yellow, and homogeneous. These were bordered by a narrow zone of hemorrhage. The scarring in the septum was quite marked, and large areas of fibrosis were seen, which obviously had followed previous patches of necrosis.

The coronary arteries were remarkably thin and delicate. About 1 cm. below its point of origin, the anterior descending branch of the left coronary was distended, and its lumen was filled for a distance of 1 cm. by a greyish red mass, which slipped

out with great ease, and was not attached to the wall at any point. No similar mass was found in any other branch of the coronary arteries.

There were numerous infarcts in both lungs.

Microscopic Examination—

Heart (Right Auricle and Left Ventricle): The muscle fibers were very irregular in arrangement and appearance. They were large in size. Most of them were vacuolated, and this feature in many places was so pronounced that only a little remnant of sarcoplasm remained against the cell membrane, mak-

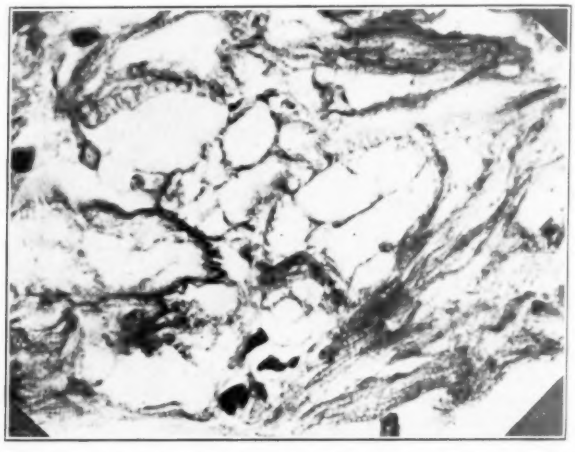

Fig. 5.—(Case 2) Hydropic degeneration of heart muscle fibers. Note the extreme vacuolization and almost total absence of sarcoplasm. Hematoxylin and eosin; ×720.

Fig. 6.—(Case 2) Hydropic degeneration of heart muscle fibers, most of which are cut transversely. Vacuolization is less marked than in Fig. 5. Hematoxylin and eosin; ×720.

ing the muscle fibers appear as empty envelopes. The nuclei varied greatly in size. Many were exceedingly large and contained an unusual amount of chromatin; others had an hydropic or vacuolated appearance. The nucleolus in some of the nuclei was very prominent; in others, it had a pale, watery appearance, and occasionally was swollen and stained with eosin. The myofibrils, when seen, were very coarse. In many places were large amounts of connective tissue, which was compact and dense, with but few blood vessels in it.

Fat Stain (Scharlach R.): A small amount of fat was present within some of the muscle fibers, but the clear material in the muscle which gave the vacuolated appearance did not stain.

Interventricular Septum: The same vacuolization and enlargement of the muscle fibers was shown in this preparation. The nuclei were distinctly enlarged and very hyperchromatic. Many were vacuolated and apparently in the process of degeneration. An irregular scar, composed of moderately dense, vascular connective tissue, extended down from the endocardium into the muscle for a considerable distance. Its position suggested that it must interrupt the conduction system. In one area, there was a large mass of muscle undergoing necrosis. The nuclei had practically disappeared. The striations, however, could be vaguely seen. Large phagocytic cells with vacuolated cytoplasm were collected about the infarct and were penetrating into the necrotic muscle cells.

The clot in the right ventricle showed the typical structure of a thrombus.

The mass from the anterior descending branch of the left coronary artery proved to be a recent thrombus.

The aorta showed no intimal thickening. With the van Gieson stain, the elastic fibers appeared to be large and well preserved. The media and adventitia were

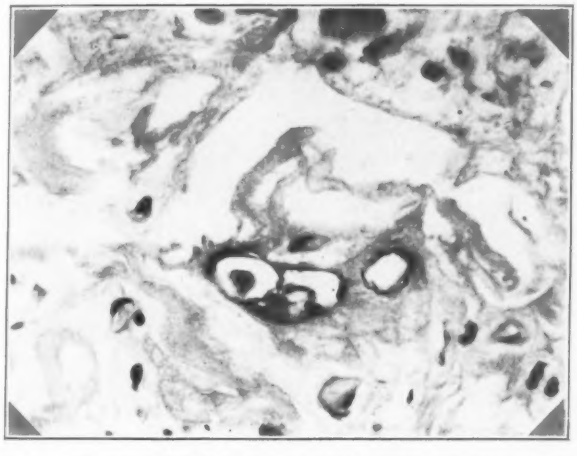

Fig. 7.—(Case 2) Nuclear degeneration of heart muscle fibers. The chromatin is concentrated at the margin of the nucleus. Hematoxylin and eosin; ×720.

normal. The von Kossa stain for calcium was negative. There were no changes in any of the smaller vessels, including those in the kidneys.

Many of the alveoli of the lungs contained fresh blood and frequently groups of large mononuclear cells containing hemosiderin were collected in the alveoli. The capillaries of the septa were engorged, but did not bulge into the alveolar space, as in chronic passive congestion. The larger vessels were normal. The pleura was of normal width and appearance. In one section appeared a characteristic infarct.

Anatomical Diagnosis.—Cardiac hypertrophy and dilatation; hydropic degeneration of the heart muscle; fibrosis of the myocardium; infarcts of the heart, old and recent; thrombi in the right ventricle; infarcts of the lungs; right hydrothorax; embolus of the anterior descending branch of the left coronary artery.

Final Note.—A case of extreme cardiac hypertrophy in a young man. The changes in the heart muscle were unique. The muscle had apparently undergone a marked hydropic degeneration, and a similar process affected the nuclei. No cause could be found to explain this. There were also recent and old infarcts and an embolus in the anterior descending branch of the left coronary artery.

CASE 3.—Unit No. 81203. G. T., colored male, married, aged thirty-one years, was admitted to the surgical service on May 10. He had been a rock-driller for ten years. He complained of a painful swelling in the right groin, which had been present for three weeks, and which he first noted two days after a drinking bout. There were no cardiac symptoms.

His mother died of heart trouble. He gave an indefinite history of "rheumatism" in the right hip fourteen years previously, which lasted for two weeks and never recurred. He had gonorrhea at fourteen. He had never had a serious illness. He smoked two packages of cigarettes a day and rarely took alcohol. He had been married for two years. There were no children.

It was noted that the heart was enlarged to the left, the apex impulse being seen and felt 12 cm. from the median line in the fifth space. The sounds were of poor quality, and a soft systolic murmur was heard at the apex. The blood pressure was 100/60. The Wassermann reaction of the blood was negative. The leucocyte

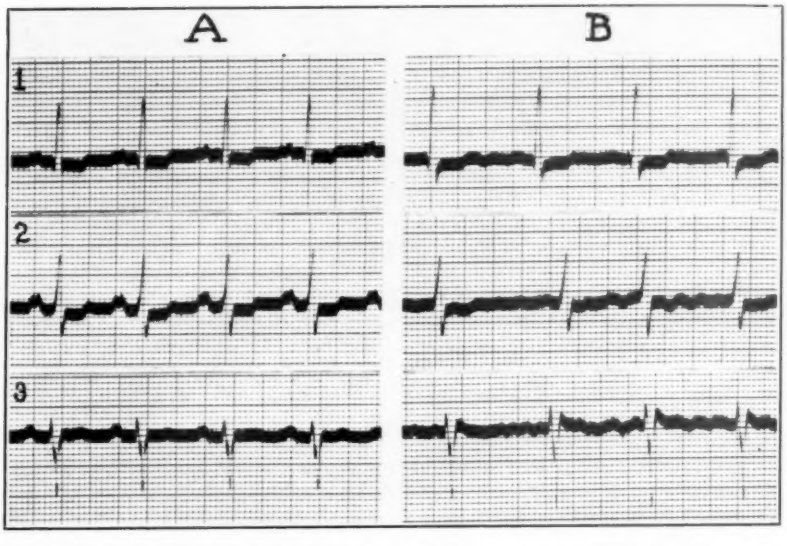

Fig. 8.—(Case 3) *A*. September 19, two weeks after the second admission to the hospital. Regular sinus rhythm, with rate of 94 and left ventricular preponderance. P-R (conduction) time is 0.15 second. The T-wave is inverted in Lead I, diphasic in Lead II and upright in Lead III. Three days previously digitalis, 0.8 gm., was given. Graphic signs of cardiac damage are relatively slight.

B. November 14 (six weeks before death). Auricular fibrillation, with rate of 72. There is but little change in the general form of the complexes.

count was 9,700, with 70 per cent polymorphonuclears. The urine contained neither albumin nor sugar. X-ray films of the chest showed no areas suggesting tuberculous infiltration, but the heart shadow was seen to be enormously enlarged, particularly to the left.

A mass of infected glands in the right inguinal region was incised and drained. Microscopic examination of a bit of tissue removed at operation showed no tubercles and no caseation necrosis. A definite diagnosis of tuberculous adenitis could not be made. The patient was discharged on May 19, with a granulating wound.

Two weeks later, he entered the city tuberculosis sanatorium, at Seaview, where he remained for two and one-half months. While there, an inguinal hernia was repaired. He gained ten pounds and was told that he did not have pulmonary tuberculosis. The night before he left this institution, he had his first attack of dyspnea,

and was unable to sleep because of difficulty in breathing. In spite of this fact, he soon returned to his job, but after working for one day he again had a sudden attack of shortness of breath, and was obliged to stop. Dyspnea continued, and palpitation and precordial pain appeared. On September 2 (three and one-half months after leaving the hospital and three days after resuming work), he was readmitted to the ward.

On admission, he was quite short of breath and looked ill. The temperature was 101.2° F. The left tonsil was moderately large, but did not appear to be infected. There were coarse râles scattered throughout both lungs. The heart was greatly enlarged to the left. The rate was 104. The rhythm was regular and the sounds of fair quality. There was a soft systolic murmur at the apex. The blood pressure was 98/72, but had risen on the following day to 106/86. There was slight clubbing of the fingers. The liver and spleen were not enlarged. Blood count showed: R.B.C. 4,260,000; hemoglobin 80 per cent; leucocytes 7,800, with 64 per cent polymorphonuclears. The Wassermann reaction of the blood was again negative. The sputum, on culture, yielded many influenza bacilli and numerous colonies of *Staphylococcus aureus* and nonhemolytic streptococcus. No tubercle bacilli were found at any time. The blood urea was 26 mg. per 100 c.c. Numerous blood cultures were negative. X-ray films of the chest showed patchy areas of density in the lower third of the right lung, suggesting pneumonic consolidation. The heart shadow was enormously enlarged. There was a good deal of peribronchial thickening, which was attributed to congestion of circulatory origin. The electrocardiogram showed sinus tachycardia, with rate of 120, and well-marked left preponderance. The P-R interval was 0.15 second. The T-wave was inverted in Leads I and II, and upright in Lead III. Inversion of T_1 and T_2 suggested myocardial damage (Fig. 8).

There was continuous elevation of temperature, with fluctuations from 98 to 104.8° F. There was also sustained tachycardia, the rate usually ranging between 90 and 110. Sinus tachycardia persisted until November 14, when auricular fibrillation, with rate of 72, was observed. Four days later, sinus rhythm reappeared. The leucocytes were never greatly increased, the highest count recorded being 12,000, with 85 per cent polymorphonuclears; they were usually under 10,000. There was no significant change in red cells or hemoglobin.

On September 12 (ten days after admission) he complained of sudden blindness in the left eye, and it was apparent that there had been an embolus in the central artery of the retina. Subsequently, expectoration of blood and pain in the left lumbar region suggested infarction of the lungs and left kidney. The blood pressure remained low—100 to 108 mm. systolic; 64 to 88 mm. diastolic. Aspirin, in large doses, appeared to have a mild antipyretic effect at times. The signs and symptoms of cardiac insufficiency gradually increased and were uninfluenced by digitalis, given at first in full dosage, and later as a maintenance ration. Congestive heart failure became extreme and a cardiac psychosis developed. He died on December 30 (4 months after admission), of advanced cardiac insufficiency.

Autopsy No. 10368.—The autopsy was performed by Dr. D. H. Andersen. On external examination, the striking feature was marked edema of the legs to the thighs, and also of the hands. The supraclavicular and axillary lymph nodes were moderately enlarged. There was slight clubbing of the fingers.

Thoracic Cavity: The pericardial sac contained 200 c.c. of clear, blood-tinged fluid. The heart occupied an area measuring 12 cm. in its vertical diameter, and 16 cm. in its transverse diameter. The right pleural cavity contained 900 c.c. and the left 400 c.c. of blood-tinged fluid.

Heart: The heart weighed 640 grams. The visceral pericardium was dull and there were a few small deposits of fibrin over both auricles and ventricles. These deposits were especially marked at the apex of the left ventricle. Over the upper,

anterior portion of the right ventricle, there was a white, opaque patch of thickened pericardium, about 2 cm. in diameter. The right auricle was not enlarged. The foramen ovale was closed save for a narrow, slit-like opening along the anterior margin. The tricuspid valve was composed of four leaflets, the extra leaflet being formed by the division of the marginal segment into two leaflets of approximately equal size. There was slight edema along the margins of the valve. There was thickening and lengthening of the chordae tendineae and moderate hypertrophy of the papillary muscle. The right ventricle was markedly dilated, especially in the region of the conus, below the pulmonary valve. There were thin streaks of endocardial thickening over the interventricular septum, and along the anterior wall of the ventricle. The interventricular septum bulged to the right. Numerous small, mural thrombi occupied the entire apex of the right ventricle. These appeared to be organized, and the subjacent muscle wall was thinned out. The left auricular wall was hypertrophied. There was slight, marginal thickening of the mitral cusps, particularly of the anterior leaflet.

The left ventricle was greatly hypertrophied and dilated, giving it an almost spherical shape. The endocardium of this chamber was thickened. Many small, adherent thrombi filled the interstices of the columnae carneae at the apex. The myocardium at this point was greatly thinned out. On section, fine fibrous strands extended from below the endocardium into the muscle.

The coronary arteries showed no changes, except for slight intimal thickening of the left branch.

The aorta and systemic arteries were normal. There were infarcts in the right lung, and in both kidneys. In a number of the inguinal lymph nodes were seen small areas of scarring.

The changes in the other viscera were those characteristic of chronic passive congestion.

Microscopic Examination—

Heart: The epicardium was slightly thickened. The muscle fibers were hypertrophied and their nuclei were irregular in shape, pale and uneven. Occasional small hemorrhages were observed separating groups of muscle bundles. Along the endocardium were seen old, completely organized and more recently formed thrombi. There was no evidence of acute inflammatory change in any of the sections. Gram and Levaditi stains showed no organisms.

The mitral valve was slightly thickened, due to edema. There was no cellular infiltration.

The coronary arteries, aorta and systemic vessels showed no changes.

An inguinal lymph node showed small areas in its center, which contained pinkish, necrotic tissue. At the margin was a ring of young fibroblasts, forming a layer of even thickness about the necrotic mass. Around the fibroblastic ring were lymphocytes. A few giant cells were seen in the zone of fibroblasts.

Anatomical Diagnosis.—Cardiac hypertrophy and dilatation; mural thrombi in the ventricles; infarcts of the right lung and both kidneys; chronic passive congestion of the lungs, liver, spleen, and pancreas; bilateral hydrothorax; hydropericardium; ascites; edema of the extremities; tuberculosis of the inguinal lymph nodes; chronic prostatitis; congenital malformation of the heart (patent foramen ovale and quadricuspid tricuspid valve).

Final Note (by Dr. A. M. Pappenheimer).—The central lesion at autopsy was an enlarged heart with parietal thrombi, but without any significant valvular or myocardial lesions. The changes in the other organs were those associated with embolism and infarctions from mural thrombi and with cardiac insufficiency. In view of the patient's history of ten years of rock-drilling, one might anticipate silicotic changes. The cough and the x-ray findings were in accord with this possi-

bility, but the sections of the lung offered no support for this diagnosis. The enlarged lymph nodes in the groin, for which the patient originally entered the hospital, contained structures which resembled tubercles, but this could not be proved. The cause for the cardiac dilatation and mural thrombosis remained undiscovered. There were no clear-cut inflammatory changes other than those associated with the organizing thrombi.

DISCUSSION

Clinical Picture.—These three cases presented certain features in common. The patients were young adult males, aged respectively eighteen, twenty-nine, and thirty-one years. Two were white, one was a negro. The symptoms of onset were palpitation due to cardiac irregularity in two, dyspnea and precordial pain in the third. The duration of illness from the onset of incapacitating symptoms to a fatal termination was less than a year in all. In two instances, brief attacks of arrhythmia had been noted several years previously. Death was due to rapidly progressive cardiac insufficiency in the two older patients and to coronary embolism in the young man, aged eighteen.

The heart was conspicuously enlarged in all. There were no signs of valvular disease. The blood pressure was normal or a little below the normal. There were no evidences of arterial or arteriolar sclerosis. In each patient there occurred embolisms to the viscera—to the lungs in all three, to the kidneys in two, and to the central artery of the retina in one. In one patient, as has been stated, a coronary embolus terminated life. At autopsy, it was apparent that the emboli originated from masses of thrombi which lay within the ventricles of the heart. Fever was present for varying periods preceding death, and was probably associated with visceral infarctions.

In two cases, tachycardia and other cardiac arrhythmias played a prominent rôle in the course of events. Frequent transitions from one rhythm to another were recorded in electrocardiograms, which at times showed bizarre complexes. In the third case, the form of the graphic records deviated relatively little from the normal, and a short paroxysm of auricular fibrillation was the only form of irregularity.

Pathology.—Examination of the three hearts at autopsy revealed a number of points of similarity, as well as certain individually characteristic lesions. In the gross, enormous hypertrophy was striking, the heart weights being 740, 750, and 640 grams, respectively. There were areas of myocardial softening in two cases, especially noticeable in the region of the interventricular septum. In places, the endocardium was thickened. Thrombi lay between the columnae carneae of the ventricles and bits of clot had evidently broken off with resultant embolism and infarction in the lungs and kidneys.

There were no vegetations on the heart valves, nor was parietal endocarditis present. The aorta, coronary, and systemic arteries showed no

changes. The kidneys appeared to be normal. In no instance was the thymus enlarged.

On microscopic examination, hypertrophy of individual muscle fibers was observed in all three cases. In two, infarcts of the myocardium were seen undergoing necrosis, as well as in various stages of degeneration and repair. In other sections there were numerous connective tissue scars, representing healed lesions.

As noted in the protocol, the heart muscle cells and their nuclei in Case 2 exhibited a curious hydropic degeneration, with extreme vacuolization. Similar changes have been observed in the myocardium of patients who have died of diphtheria.[1] In Case 3, only a few hemorrhages were seen between the bundles of hypertrophied muscle cells.

There were no inflammatory changes other than those associated with organizing thrombi. A diligent search was made for lesions suggestive of rheumatic fever, syphilis, or arteriosclerosis, but none were found.

Etiology.—The histories and clinical data afford no clues as to etiology. Even in the light of the post-mortem examinations, the cause for the cardiac enlargement and mural thrombosis remains obscure. With such imperfect knowledge, it is impossible to say whether these cases represent a single condition, perhaps at various stages of its evolution; or whether we are dealing with three persons whose hearts have reacted in similar, though not identical, fashion to entirely different harmful processes or agents. At present, it is difficult to bring into association the diverse lesions found in the myocardium on microscopic examination; yet similarity of many of the essential features, both clinical and pathological, lends support to the belief that the three cases may be regarded as bearing a relationship to one another.

A discussion of possible pathogenetic factors must, of necessity, be purely hypothetical and it is apparent that no definite conclusions can be formulated. The rôle of prolonged, violent exercise or of excessive fluid intake seems excluded by the histories. There were no abnormalities in the origin or distribution of the coronary arteries.

That the cardiac enlargement may be the result of a congenital anomaly is suggested by certain points of resemblance between these cases and instances of "idiopathic hypertrophy of the heart" in children, of which some fifty adequately described examples are on record. A number of these young patients have not manifested any symptoms until they were several years of age, and this, as Howland[2] has said, would make it seem possible if not probable, that the hypertrophy has been late in developing. In one of the children reported by him, there were no signs of cardiac disorder until the age of four. Most of these youngsters, however, have not survived for many months, and the final catastrophe has been of short duration, a matter usually of a few days or weeks. Examination of many of the hearts at autopsy has shown

but little other than hypertrophy of the fibers; and some observers would exclude from the group those cases exhibiting further changes in the heart muscle. In a number of instances in which the established criteria were otherwise satisfactorily met, lymphocytic infiltrations between the muscle bundles have been found. In more recent accounts there have been described, in addition, areas of degeneration and necrosis in the myocardium, with replacement fibrosis and endocardial thickening;[3, 4] hydropic degeneration of the heart muscle cells;[5] and vacuolization of these cells, which was regarded as distinctly abnormal and of unknown origin.[6]

In our own cases it is conceivable that the condition, if the result of congenital predisposition, may not have developed until later in life. How long hypertrophy was present prior to the onset of discomfort, is not known. The rapid increase in the severity of the symptoms, as well as the character and extent of the lesions at autopsy, point to a progressive process. It is of interest to note that minor congenital malformations were present in two of our patients; namely, a common origin of the innominate and left common carotid arteries, and anomalous fissuration of the lungs in Case 1; partial patency of the foramen ovale and a quadricuspid tricuspid valve in Case 3.

Whereas at the bedside an infectious origin was suspected, no evidence in support of this notion was present at autopsy. The resemblance of the hydropic degeneration of the muscle fibers to the lesions sometimes found in diphtheria has already been mentioned. No lead was obtained pointing to any specific causative bacterial agent or virus; and the usual changes associated with inflammation were conspicuously absent. There were no cellular infiltrations such as characterize acute interstitial myocarditis of the Fiedler type.

In a search of the literature, only two cases were encountered which might be regarded as bearing some resemblance to those here described. Laubry and Walser[7] observed a robust youth, aged fifteen years, who died suddenly within three months after the onset of anorexia and dyspnea. There was no history of antecedent disease. The symptoms of cardiac insufficiency were rapidly progressive and were unresponsive to the usual therapeutic measures.

At autopsy, the heart weighed 490 grams. The myocardium was pale and flabby. There were no valvular lesions or intracardiac thrombi. A large infarct was present in the lower lobe of the right lung. The aorta was normal. Microscopically, the heart muscle showed only a mild degree of interstitial edema. There were no pathological changes in the other organs.

To this form of cardiac insufficiency without apparent cause, Laubry applied the term "myocardie." Walser[8] again reported the same case in the monograph submitted for his thesis and endeavored to enlarge

upon the concept. But he added no relevant clinical material controlled by post-mortem examination.

The second case was described by Whittle.[9] A twenty-year-old student at Cambridge, England, suddenly fell dead while riding his bicycle. Post-mortem examination revealed a huge heart, which weighed 840 grams. The valves, endocardium, and coronary arteries were normal. The thymus weighed 30 grams. The aorta was quite delicate and of small caliber, measuring 16 mm. at the beginning of the descending portion (the average normal aorta at this level measures 23 mm.). There were flecks of early atheroma near its origin. An acute tracheitis was present. Microscopic examination of sections of the left ventricle showed cloudy swelling, with loss of regular striation of the fibers. There were no foci of necrosis, degeneration, or inflammation. The kidneys were normal. There were no changes in the systemic arteries or in the arterioles of the viscera.

The history revealed little. He had been healthy and lived a normal life. He had done much cycling over long distances, but no racing. There was no evidence of indisposition prior to death. The level of the blood pressure was not known.

The great size of the heart remained entirely without explanation. The large thymus and hypoplastic aorta were not considered to be primary causative factors. Cloudy swelling of the heart muscle fibers was ascribed to a toxic effect of the acute tracheitis. Whittle regarded the prolonged muscular exertion of cycling as an important element in inducing the cardiac hypertrophy. But such an interpretation of the facts leaves many obvious questions unanswered.

Diagnosis.—During life, prominence of the cardiac manifestations in all three cases suggested rheumatic fever as the most likely etiological diagnosis. Elevations of temperature, systolic murmurs, and frequent changes in the form of the electrocardiogram tended to support this idea. In the first case, because the patient had lived in South America, diagnostic consideration was given to the cardiac form of American trypanosomiasis, as described by Chagas. In this case also, coronary disease and syphilis were mentioned as the basic pathological states. In the third patient, clubbed fingers and the numerous embolic phenomena brought up the possibility of subacute bacterial endocarditis. This man was a negro and biopsy of an enlarged inguinal gland showed structures resembling tubercles; hence, it was inferred that tuberculous pericarditis might be present, perhaps with adherent pericardium. He had also been a rock-driller for ten years. It was not unreasonable to suspect silicotic changes in the lungs, to which the cardiac disturbances were secondary.

For the present, the diagnosis, if made during life, must be arrived at by exclusion. It is not known whether these cases are unrelated in their pathogenesis or represent different phases of a single disease

process. In the absence of such knowledge and of the etiology, it would serve no useful purpose at this time to attempt to define diagnostic criteria. It is hoped that further observations will throw added light on this unusual form of cardiac enlargement.

SUMMARY

Three cases have been described presenting an unfamiliar clinical picture. The main features were great cardiac enlargement, intraventricular thrombosis with embolisms to the viscera, and death within a year after the symptoms were well established. There were no signs of valvular disease or arteriosclerosis, and the blood pressure was at the normal level or slightly below it. Microscopic examination of the myocardium showed hypertrophy of muscle fibers in all, infarcts in varying stages of degeneration and repair in two, and in one of these, a curious hydropic degeneration of the heart muscle cells with vacuolization of the sarcoplasm. The third case showed only a few hemorrhages between the muscle bundles. No inflammatory changes or signs of arteriolar disease were observed.

Though clinically the patients presented many essential features in common, the lesions at autopsy were not identical. It was not possible to state whether these cases represented a single condition at different phases of its development or were entirely unrelated in their pathogenesis. The etiology remained obscure.

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THE HEART IN MYXEDEMA, WITH A REPORT OF TWO CASES*

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SINCE the original observations of Zondek[1] in 1918 on the so-called myxedema heart, considerable literature has accumulated describing the cardiac sequences resulting from the myxedematous state. From the studies reported by various authors conflicting opinions have arisen concerning the extent of damage to the heart in the course of the disease. Although several authorities have questioned the very existence of a cardiac syndrome associated with myxedema, it is now well established that protracted cases in some instances will produce gross signs of myocardial insufficiency. The controversy appears to be centered about the question of the frequency of heart failure in myxedema. Lerman, Clark and Means[2] are of the opinion that congestive failure in myxedema is rare, while Fahr[3] contends that the incidence of heart failure associated with the disease is high.

Because of the inconstancy of heart failure in reported cases of myxedema, I have approached the study of the problem from an angle somewhat different from that of previous investigators in an attempt to determine when true heart failure exists in myxedema. The opportunity for the study was afforded by two typical cases of myxedema in each of which the outstanding symptom was dyspnea. Case 1 presented the findings of a gross congestive failure of a moderate degree. In Case 2 this feature was entirely lacking; yet further studies indicated that myocardial insufficiency was actually present.

REVIEW OF LITERATURE

As already mentioned, myxedema heart was first recognized as a clinical entity by Zondek[1] in 1918 who reported four unusual cases of myxedema in which he could demonstrate cardiac enlargement with sluggish cardiac movements, accompanied by bradycardia and alterations in the electrocardiogram. He not only demonstrated the existence of a generalized cardiac dilatation but also observed a remarkable diminution in the transverse diameter of the heart and a return of the electrocardiogram to its normal contour following the administration of thyroid extract. A reduction of 5.7 cm. in the transverse diameter of the heart was noted in one of his cases after eight weeks of thyroid therapy. Since his original observation, corroborative evidence has accumulated in the literature to justify the term myxedema heart as a

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distinct clinical entity in heart disease. Thus Assman[4] in 1919 reported a case of myxedema heart, the findings in which conformed in all respects to those of Zondek. This observer showed that digitalis was ineffective upon the heart failure in myxedema. However, when thyroid therapy was instituted in this case, marked clinical improvement of the myxedema and of the heart failure was noted. The transverse diameter of the heart decreased 4 cm. In 1920 Meissner[5] reported three cases of myxedema. Following thyroid therapy there was a shrinkage of 4.5 cm. in the transverse diameter of the heart as shown by the teleroentgenogram. The second case was complicated by a chronic nephritis with a systolic pressure of 180. After two months of thyroid therapy, a marked clinical improvement was observed, although subsequent x-ray studies showed no actual shrinkage in the size of the heart. The third case studied showed no cardiac enlargement. In 1924 Laubry, Mussio-Fournier and Walser[6] reported a case of myxedema associated with anginal attacks. Orthodiagraphic studies disclosed cardiac dilatation. Again in this case, when digitalis was administered, no relief was noted, but when thyroid medication was initiated, marked clinical improvement with a reduction in the size of the heart was soon apparent. In 1925 Fahr[7] reported three cases of myxedema. In his first case, he showed that the administration of digitalis, rest in bed, and fluid restrictions had very little therapeutic effect in ameliorating the symptoms and signs of heart failure. However, when thyroid therapy was instituted, the signs of congestive failure promptly cleared up. In one of his cases, after a period of seven weeks under thyroid treatment, the transverse diameter of the heart decreased from 19 cm. to 12.7 cm. The electrocardiogram, which originally showed a left axis deviation, negative T_1, and iso-electric T_2 with a QRS spread of 0.18 sec., also became normal. He was further able to show that after the withdrawal of thyroid, not only did the signs of myxedema reappear, but also that the heart again dilated so as to produce signs of cardiac insufficiency. Curschman[8] in 1926 also described a case of myxedema with cardiac dilatation and congestive heart failure which responded readily to thyroid medication. In 1929 Duden[9] reported a case of myxedema with myocardial failure which disappeared following the administration of thyroid. A recession of 3.5 cm. in size of heart was observed after a period of six weeks. In 1931 Davis[10] confirmed the results obtained by Fahr. He reported that after the restoration of the heart to its normal size under thyroid regime, the heart would dilate and signs of congestive failure reappear if thyroid was withdrawn. He showed further that the heart would again return to its normal size, with the disappearance of heart failure, upon the readministration of thyroid. This he could not accomplish with digitalis. This phenomenon of dilatation and return to normal suggested to Dr. Moses Barron[11] the term "accordion heart."

Cases of myxedema without congestive failure but with diffusely dilated hearts have been reported. Zins and Rösler[12] in 1926 were able to demonstrate a shrinkage of 3.3 cm. in the transverse diameter of the heart after three weeks of thyroid therapy. Similarly, Schittenhelm and Eisler[13] in 1927 reported a reduction in the transverse diameter of the heart from 18 cm. to 14.7 cm. in a period of eleven days after intravenous administration of 12 mg. of thyroxin. The electrocardiogram also returned to normal in this short period. In 1929 Holzman[14] reported a case very similar to that reported by Meissner[5]—that of a man fifty-eight years of age who presented the typical signs and symptoms of myxedema. The heart was enlarged both to the left and to the right as seen in the x-ray film, while the electrocardiogram showed a low voltage in all leads with left axis deviation and abnormal QRS complexes in all leads. Marked clinical improvement of the myxedematous state was observed following adequate dosage of thyroid, yet no demonstrable changes were noted in the graphic records, nor was there any appreciable reduction seen in the x-ray outline of the heart.

The existence of the cardiac syndrome of myxedema heart has been challenged by several authorities. Christian,[15] in a comprehensive study of thirty cases of myxedema in 1925, was unable to find a single case which exhibited evidence of congestive failure with a picture of a generalized cardiac dilatation as described by Zondek, Assman and Fahr. Willius and Haines,[16] after studying 162 cases of myxedema with particular reference to the status of the heart in myxedema, were unable to justify the establishment of a cardiac syndrome of myxedema. Means, White and Krantz[17] studied forty-eight cases of myxedema with special reference to the cardiac signs. They found only one case which showed the classical signs of cardiac dilatation and T-wave negativity as described by Zondek. While they admitted that myxedema heart existed, they emphasized the rarity of the condition. Case,[18] in an analysis of 58 cases of myxedema, could not find a single one corresponding to Zondek's description. Ayman, Rosenblum and Falcon-Lesses[19] reported two typical cases of myxedema showing the classical signs of cardiac dilatation with changes in the electrocardiogram, but found no evidence of cardiac insufficiency. Lerman, Clark and Means[2] in a recent study in a series of thirty cases of myxedema were able to find only one case which showed evidence of gross congestive failure. However, they point out that four cases showed evidence suggestive of cardiac failure. One case showed crepitant râles at the lung basis and pitting edema of the extremities and the sacrum. The second case showed a small amount of fluid in right pleural cavity, pitting edema, and the liver palpable at the costal margin. The other two cases revealed crepitant râles at the lung basis, palpable liver edge, and pitting edema. All of these signs disappeared on rest and thyroid medication. Yet, they do not consider these findings conclu-

sive evidence of myocardial insufficiency as a direct result of the myxedematous state. They are of the opinion that the patients who present findings suggestive of cardiac failure usually have a coexisting hypertension and arteriosclerosis. Means[20] remarks that while the phenomena of congestive failure are rare, the characteristic enlargement described by Zondek is commonly seen. In the Massachusetts General Hospital series of thirty cases, twenty-seven under thyroid therapy showed some shrinkage in size as determined by roentgenological examination. Therefore, Means concludes, in view of the fact that some degree of dilatation is almost always present, that cardiac enlargement should be considered a part of the picture of myxedema rather than a complication.

On the other hand, Fahr,[3] in a recent study of seventeen cases of myxedema heart, concluded that 75 per cent showed some signs and symptoms of heart failure, while 30 per cent showed very severe evidence of congestive failure. Tung,[21] in an analysis of eighteen cases of myxedema, found seven cases (39 per cent) which showed signs of cardiac insufficiency. Thus there appears to be a considerable discrepancy in the incidence of heart failure in myxedema as reported by the various authors.

However, in the analysis of these Massachusetts General Hospital cases,[20] 65 per cent of the series showed dyspnea. This agrees very well with the report of Ayman and his associates who found that of twenty-two cases analyzed from the literature, 60 per cent showed shortness of breath. Whether or not dyspnea should be interpreted as a cardinal symptom of congestive failure in cases of myxedema is, of course, a matter for argument. If it were possible to analyze the dynamic events as cardiac dilatation manifests itself, it would probably be found, as Wiggers[22] believes, that the degree of dyspnea is roughly related to the decreasing efficiency of the heart. In this event, the percentage of heart failure, in the strict sense of the term, would obviously be too low in the Massachusetts General Hospital series.

CASE REPORTS

CASE 1.—White female, aged fifty-six years. Chief complaints were increasing weakness and fatigue and marked dyspnea on exertion. She dated the onset of her illness approximately six years ago. At that time, her first symptom was weakness, which steadily progressed. This was accompanied by gradual loss of ambition. She was seen then by a physician and was told that she had high blood pressure. In the past four years, her skin had become dry and scaly with a loss of hair. She also noted that she began to increase in weight in spite of the fact that her appetite was poor. During the past two years, she noted that her voice gradually became coarser and deeper in pitch. Her tongue was "always in the way" when she wanted to talk. Some impairment of hearing was noted at this time. She felt cold constantly, even during the hot summer days. For the past two years she visited a physician because of rheumatic pains in her knee joints and right shoulder. The medication given offered no relief. A bloated feeling in her abdomen bothered her

constantly. For the past year, she was forced to abandon her social activities and housework because she was becoming so sluggish and clumsy. Her memory became poor, and she appeared to take no interest in life. Especially during the last year she noted that she was becoming short of breath. It was almost impossible for her to climb the stairs and do her housework because the slightest exertion would compel her to stop and gasp for breath. During the past half year, she noticed that her ankles and legs were swollen. There was no history of thyroidectomy or thyroiditis.

Physical examination revealed a typical case of myxedema. The patient appeared listless and apathetic. Cerebration was retarded. Articulation was slow. The voice was deep and of a monotonous character. The palpebral fissures were markedly narrowed with puffy, boggy lids. The nose was broad and thick. The lips were thick and had the appearance of a reddish cyanosis. The complexion was pale and waxy with a circumscribed pinkish flush over the malar prominences. The hair was sparse and brittle. Bolsters of supraclavicular fat were present on both

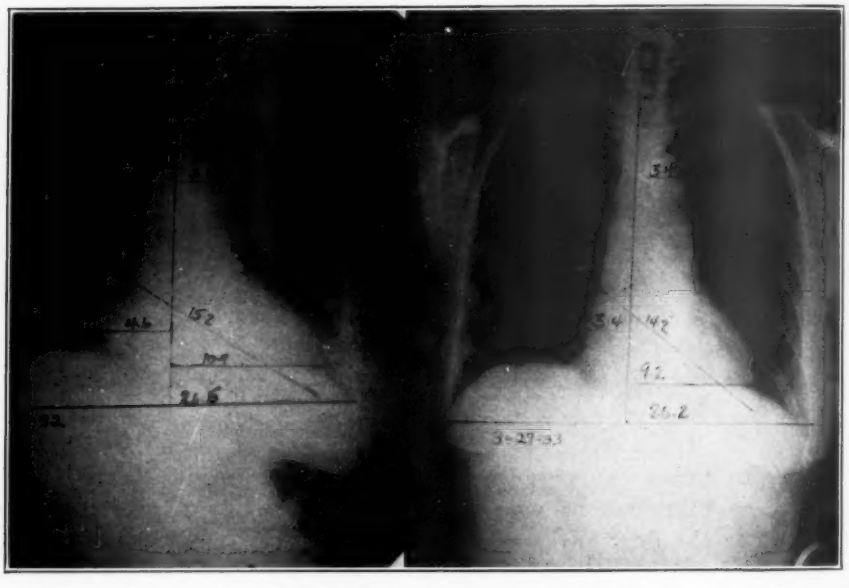

Fig. 1.—Case 1. Appearance of teleroentgenogram before and after five and one-half months of thyroid therapy. Before treatment: basal metabolic rate −36 per cent; blood pressure 160/110 mm. After five and one-half months of therapy: basal metabolic rate −1 per cent; blood pressure 135/88 mm.

sides. The skin felt cold and was thick and dry. Dyspnea on the slightest exertion was evident. The heart tones were faint. The pulse rate was 68. No murmurs were elicited. Râles were present over bases of both lung fields. The liver was palpable at the costal margin in the midclavicular line. No ascites was noted. Considerable pitting edema of the lower extremities was present. No varicosities were found. The vital capacity was 2200 c.c. The patient weighed 187 lb. Wassermann and Kahn tests were negative. Hgb. 66 per cent; R.B.C. 3,280,000; W.B.C. 6,800; P.M.N. 70 per cent; Lymph. 24; Mono. 5; Eos. 1. Urine showed a specific gravity of 1.025 with faint trace of albumin and 0-1 pus cells, and occasional hyaline casts. The plasma protein determination was above normal. B.M.R. 36 per cent. Blood pressure 160/110 mm. Six-foot plate of the heart showed a diffusely dilated heart, Ml—10.9 cm.; Mr—4.6 cm.; T—15.5 cm. Transverse thoracic diameter—26.5 cm. (Fig. 1.) The graphic record on admission (Fig. 2)

demonstrated a tendency to a right axis deviation, isoelectric T_1 with slightly positive P_1, diphasic T_2 and diphasic T_3. The QRS spread in all leads was 0.1 sec. and therefore just at the upper limits of normal. Eyeground examination showed a minimal degree of retinal arteriolosclerosis. The patient was started on 1.5 gr. of thyroid extract (Armour's) daily, and on the third day, the amount was raised to 3.5 gr. Fluids were not restricted and the patient was not put to bed.

Definite changes were observed in the graphic records one week after the institution of treatment (Fig. 2). The downward deflection of the S-wave in Lead I had returned to the normal position; the diphasic T_2 and T_3 had become definitely positive. Graphic records taken approximately one and one-half months after treatment showed a positive T in all leads, and this could be interpreted as a normal electrocardiogram.

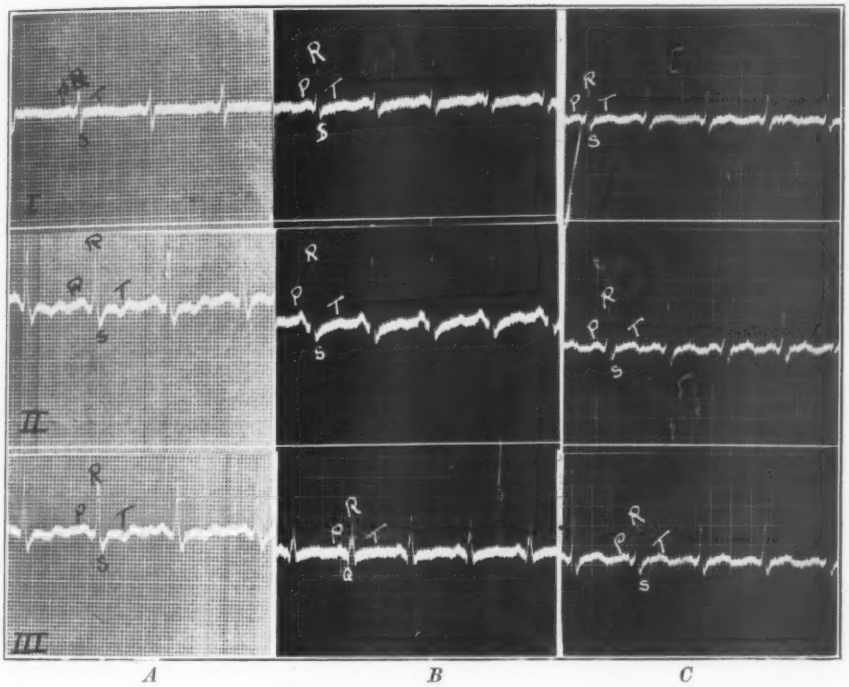

Fig. 2.—Case 1. Electrocardiographic changes: (A) before institution of thyroid therapy; (B) one week after the institution of treatment; (C) six weeks after the institution of treatment.

Teleroentgenograms showed a definite decrease in size of the cardiac shadow approximately one month after treatment. By this time a shrinkage of 1.7 cm. in the transverse diameter of the heart had occurred. It will be noted that the shrinkage occurred mainly on the right side of the heart. This is consistent with the QRS change in Lead I which occurred as early as one week after treatment. After five months of treatment, there was a total diminution of 2.9 cm. in the transverse diameter of the heart (Fig. 1).

It is also of interest to correlate the blood pressure changes with the return of the heart to its normal size. The initial blood pressure which was 160/110 mm. dropped to 140/90 mm. after one month, and to 135/85 mm. after two months of treatment. Since then it has varied slightly with the last reading. Duden[9] in 1931 reported a similar finding in a case of myxedema with myocardial insufficiency.

Before treatment, the blood pressure was recorded as 180/130 mm. After treatment, with the disappearance of the sign of congestive failure, the blood pressure dropped to 130/85 mm.

The initial B.M.R. which was −36 per cent (checked) rose to −16 per cent after four weeks, to −9 per cent after eight weeks and to −3 per cent after twelve weeks of treatment. The weight loss in six weeks was 21 pounds, from 185 to 164 pounds. The vital capacity which was 2200 on admission changed to 2600 during the same period of time.

The case has now been followed for six months. At the end of the first six weeks, marked changes were already obvious. However, a slight amount of pitting edema was still present. The marked dyspnea on exertion, as well as the pitting edema, which the patient presented when first seen, had entirely disappeared after four months of treatment. Five months after treatment, it was no longer difficult for the patient to do her housework, to climb stairs or to take long walks. Her weight now was 144 pounds. The day before her last visit to the hospital she had done a large washing, and had sawed ten pieces of cord wood.

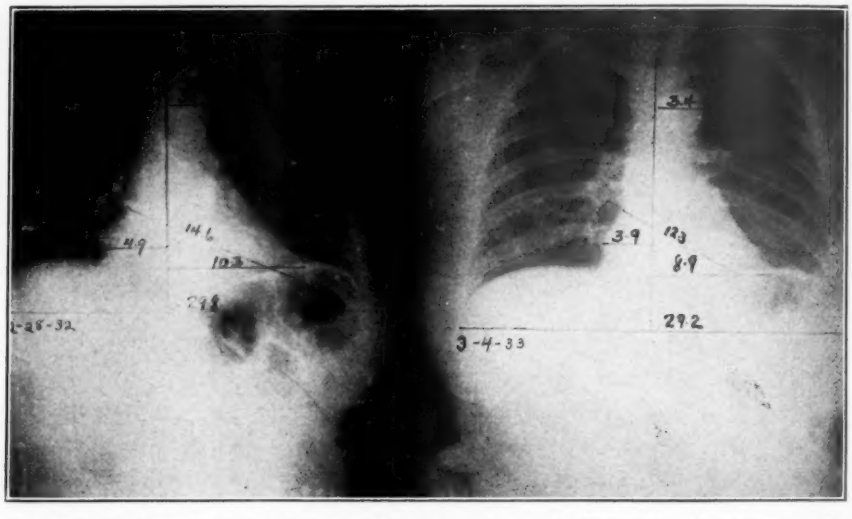

Fig. 3.—Case 2. Appearance of teleroentgenogram before and after two months of thyroid therapy. Before treatment: basal metabolic rate −30 per cent; blood pressure 130/90 mm. After two months of therapy: basal metabolic rate −4 per cent; blood pressure 130/70 mm.

Case 2.—White female, aged fifty-six years. Chief complaints were fatigue and dyspnea on exertion. Onset of trouble began about two years ago with occipital headaches and development of a "tired feeling." Then she became constipated and began to gain weight. About eight months ago, she noticed a change in voice and swelling of the face, especially around the eyes. Her skin became very dry and rough, and her hair became dry and began to fall out. Her physician treated her for nephritis without relief. During the past few months, she noticed rapid development of fatigue and impairment of memory. Her normal weight of 145 had increased to 174 pounds. She could walk only a block or two before becoming exhausted. She had difficulty in doing her simple housework. Climbing the stairs in her house was almost an impossibility because of shortness of breath. She had no history of thyroidectomy or thyroiditis. A cholecystectomy had been performed nine years ago and tonsillectomy four years ago.

While this patient did not present the classical array of signs of myxedema as in Case 1, yet there was sufficient evidence to establish a diagnosis by physical examination. There was considerable puffiness around the eyes, with moderate narrowing of the palpebral fissures. Her voice was deep and coarse and her speech was slow. There was a masklike appearance of the face. Mental torpor was not evident as in the previous case. The skin was dry and rough, but not markedly thickened. Heart tones were faint. Her temperature was 97° F. and her pulse rate 64. Weight 175 pounds. Blood pressure 130/90 mm. Basal metabolic rate −30 per cent.

The lung fields were clear. The liver was not palpable. No ascites was present. No pitting edema of lower extremities noted. The blood pressure was normal. Hgb. 90 per cent; W.B.C. 5,500. Wassermann reaction negative. Kidney concentration test showed good renal function. Very faint trace of albumin was present in the urine with 18-20 pus cells per microscopic field. Blood urea nitrogen 18.9 mg. per 100 c.c. Vital capacity 2400 c.c. Eyeground examination showed no

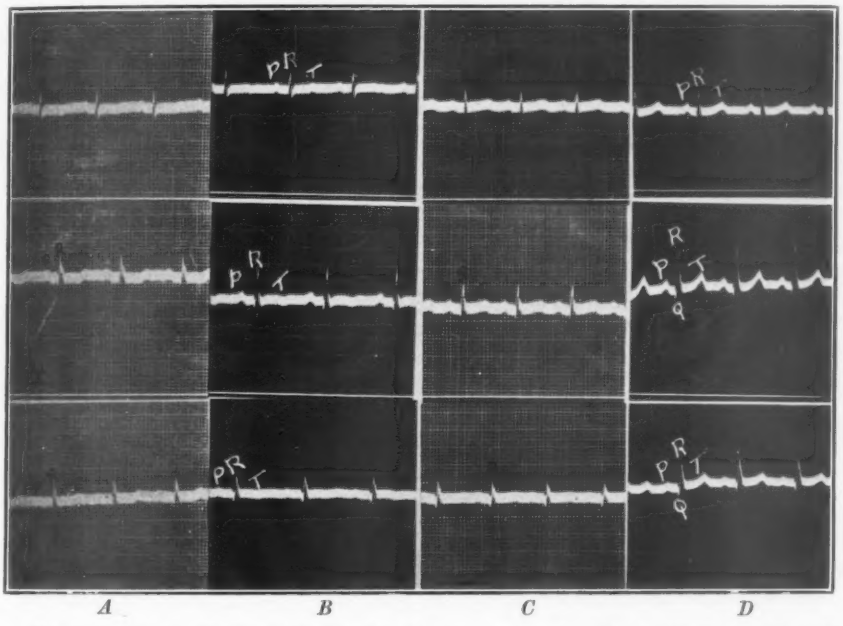

Fig. 4.—Case 2. Electrocardiagraphic changes: (A) before the institution of thyroid therapy; (B) nine days after the institution of treatment; (C) two weeks after the institution of treatment; (D) eight weeks after the institution of treatment.

arteriolar changes. The graphic record (Fig. 4) showed low voltage in all leads (under 5 mm.) with slightly negative T_1. The six-foot plate showed a diffusely dilated heart, Ml—10.3 cm.; Mr—4.9 cm.; total diameter—15.2 cm. Total transverse thoracic diameter—29.8 cm. (Fig. 3). The patient was placed on 1.5 grains of thyroid extract daily, and on the third day the dosage was raised to 4 grains.

Graphic record (Fig. 4) taken nine days after institution of thyroid therapy showed an increase of 3.5 mm. in the amplitude of the QRS complex in Lead II. After two weeks of therapy the T_1 became positive. After eight weeks of treatment, the height of the T-waves as well as the amplitude of the QRS complexes increased in all leads. Appreciable changes in the size of the cardiac shadow were noted after a period of a month. Thus the transverse diameter of the heart regressed 1.7 cm. At the expiration of two months, the total shrinkage in the transverse diameter of the heart was 2.4 cm.

A slight variation was noted especially in the diastolic pressure. On admission, the blood pressure was 130/90 mm.; after the first month 125/75 mm.; and at the end of the second month 130/70 mm. This, together with the blood pressure changes noted in Case 1, is in accord with the variations reported by the Boston investigators[2] who observed a drop of 10 mm. or more in the diastolic pressure in fourteen cases following the administration of thyroid. The rise in the basal metabolic rate was striking. The basal metabolic rate changed from a −30 per cent to −4 per cent (checked) in period of one month.

Before the institution of thyroid therapy, the minute volume was 3.4 liters.* It was checked the following day and the value was 3.6 liters. After two months of thyroid treatment, the minute volume had increased to 4.4. The initial vital capacity which was 2400 c.c. rose to 2600 c.c. after a month of treatment. This is in close agreement with the findings of Blumgaard and his associates[23] who found no significant changes in the vital capacity after thyroid treatment. In their series of cases of myxedema not one showed gross evidence of congestive failure.

This case has been followed for two months. The patient's dyspnea has entirely disappeared, and she can now carry on her routine housework without the slightest difficulty.

THE INTERPRETATION OF ELECTROCARDIOGRAPHIC CHANGES IN MYXEDEMA

The absence of the thyroid hormone may give rise to a number of disturbances in the cardiac conductive mechanism. That these graphic manifestations are not due to intrinsic alterations in the myocardium but rather to an impairment in the electrical conductivity of the myxedematous skin was the contention first advanced by Leug.[24] Nobel, Rosenblüth and Somet[25] were also of the opinion that increased resistance due to myxedematous infiltration in the skin and subcutaneous tissue could explain some of the alterations in the graphic records. It appears from recent work that such is not the case. The contour, time relations and amplitude of the auricular and ventricular complexes are fundamentally initiated in the heart and are not expressions of pathological changes in the skin. In order to determine whether the T- and P-wave alterations occurred in other abnormal skin conditions, I studied the graphic records of a case of generalized scleroderma—a condition in which there is profound infiltration in the skin and subcutaneous tissue. In this case the T- and P-wave deflections were of normal contour and amplitude. Likewise, in two cases of generalized ichthyosis, the T- and P-waves showed no abnormal alterations. However, it remained for White,[26] who employed needle electrodes, to show conclusively that the altered conductivity of the myxedematous skin had no influence on the graphic records. Reid and Kenway[27] have shown further that lower metabolic rates themselves, without myxedema, cannot give rise to definite electrocardiographic changes. True myxedema must be present to have the characteristic changes. The preponderance of evidence therefore supports the origi-

*The writer is indebted to Dr. A. C. Kerkhof who performed minute volume studies in Case 2, using the acetylene gas method of Grollman.

nal conception set forth by Zondek[1]—that the fundamental changes are essentially a result of a disturbance in the conductive mechanism of the heart.

The most frequent alterations seen in the electrocardiogram in myxedema heart are the flattening and the inversion of the T-waves which are usually seen in Leads I and II. Twenty-three out of twenty-four cases from the Massachusetts General Hospital[16] showed a low T-wave, while nine showed low voltage, and abnormal axis deviation. In Fahr's series[3] the majority of cases showed negative T-waves in Leads I and II. Thacher and White[28] in a series of fourteen cases showed a flattening of the T-waves in Lead I in all of their cases. The P-R intervals in these cases were usually normal, while the QRS complexes in several instances showed a low potential. They also observed a marked correlation between the height of T-waves and the level of basal metabolic rate. By no means are the changes limited to the T-waves. Zondek[1] found low and absent P-waves. Ziskin[29] in 1930 reported a case which showed a delayed P-R interval. The case reported by Davis[10] showed not only a flat P- and T-wave, but also a prolonged P-R interval varying from 0.20 sec. to 0.22 sec. In this same case, the axis deviation was normal before thyroid therapy, but after thyroid, the patient developed a left axis deviation. Tung,[21] after a study of 18 cases of myxedema, found P- and QRS waves of relatively small amplitude. However, the most striking abnormality in Tung's series was a flattening and inverting of the T-waves. After thyroid treatment, these abnormalities disappeared in the graphic record of 7 cases. In the case reported by Gardner[30] an abnormal spread of the QRS_1 was noted which returned to its normal limits under thyroid treatment. In my cases reported above, the electrocardiographic changes were striking. Case 1 showed an abnormal downward deflection of the S-wave in Lead I, and iso-electric T_1 and a diphasic T_2. After a week of thyroid extract, the graphic record showed a normal axis deviation and an upright T_2. The T_1 which was still iso-electric became positive after two weeks of thyroid therapy. In Case 2, before treatment, the graphic record showed a low voltage in all leads with a flat T_1. The only change noted after a week of thyroid therapy was an increase in amplitude, particularly in Lead II where the voltage increased 3 mm. After a period of two weeks, the T-waves in Leads I and II were definitely positive. It was interesting to note in the serial study of the graphic records in Case 2 the progressive increase in height of the T-waves, especially in Leads I and II. That such a condition obtains in normal individuals has recently been shown by McGuire and Foulger[31] in which they administered large daily doses of thyroid extract to four normal individuals and observed an increase in the amplitude of the T-wave.

What is the peculiar nature of the pathological condition in the myxedema heart in order that it may give rise to the various phenomena

observed in the electrocardiogram? That the auricles as well as the ventricles can be involved is evident by the changes that can occur in the behavior of the P-wave. The fact that all chambers of the heart are dilated also speaks decidedly in favor of a generalized disturbance. No doubt the morbid process is a fairly well disseminated one. However, experimental work on thyroidectomized sheep and goats shows that arteriosclerosis, as well as cardiac dilatation with a flabby condition of the myocardium, frequently accompanies the myxedematous state (Goldberg[32]). Many cases of myxedema are accompanied by disease of the coronary arteries, as was pointed out by Fishberg,[33] who found considerable arteriosclerosis in his cases post mortem. The frequency of arteriosclerosis may be explained by the fact that most of the patients with myxedema heart have already reached the age when arterial disease is common. The fact, however, that most of the graphic records assume their normal contour after thyroid treatment suggests that the disturbance in the conductive mechanism is essentially a physiological one, rather than permanent damage resulting from a coexisting coronary disease. Should coronary disease superimpose itself on a myxedema heart or vice versa, it is very questionable whether the graphic record would ever return to its normal form after thyroid therapy.

Autopsy evidence concerning the pathological condition of myxedema heart is very meager. It is possible to conceive a myxedematous infiltration being present in the heart muscle as well as in the skin and other tissues. Recent autopsy evidence indicates that something of such a nature actually occurs. Of the four cases of myxedema heart that came to autopsy at the Massachusetts General Hospital, three showed edema of the heart muscle with fibrosis; the fourth showed interstitial edema. On the basis of this evidence, it is not at all difficult to understand the rapid and striking changes seen in the graphic records following the administration of thyroid extract. The nature of the myxedematous fluid has been studied by Boothby and his associates.[34] They have shown that myxedematous patients when given thyroxin excrete in the urine a certain amount of nitrogen and that the nitrogen thus lost bears at the same time a relation to the weight loss. They conclude that the apparent edema which gave rise to the term myxedema is due to the disposition in the interstitial tissues of fluid containing about 2 per cent of nitrogen as protein. It is thus apparent that thyroxin mobilizes the myxedematous fluid and perhaps by some physicochemical mechanism removes it gradually from the heart muscle. Furthermore, recent experimental evidence shows that thyroxin acts directly on the heart muscle and by doing so increases the amplitude and strength of the heart beat.[34, 35, 36] It is probable, then, through the operations of these combined mechanisms, that the normal electrical potential differences of the conductive apparatus are slowly reestab-

lished. However, another important mechanism which is set up indirectly by the action of the thyroid extract comes into play. A myxedema heart is a generally enlarged flabby structure contracting sluggishly in the face of a diminished metabolism and oxygen deficiency. It is obvious that a myocardial anoxemia resulting from a diminished blood flow is present. This factor alone may be sufficient in itself to give rise to changes in the auricular and ventricular complexes. Following the inauguration of thyroid treatment, the minute output of the heart increases. This in turn augments coronary flow (Anrep and Segall[38]) and thus restores a more adequate oxygen supply to the oxygen-deficient myocardium. That such a mechanism may operate very soon after the beginning of thyroid therapy could well explain the early changes which occur in the graphic records of the above two cases.

On this same basis it is possible to explain the danger of promiscuous thyroid treatment in myxedema heart where coronary narrowing from arteriosclerosis is suspected. Because the great increase in minute volume and blood velocity associated with the elevation of the basal metabolic rate involves a corresponding increase in the amount of work done by the heart, the oxygen requirement of the heart muscle is increased. This demand is normally met by an increase of blood supply consequent upon increased coronary flow. When the volume of coronary flow is reduced, because of coronary narrowing and failure of the coronary vessels to dilate, serious damage to the heart muscle may ensue. This may at times terminate in coronary occlusion with fatal myocardial infarction.[3] Moreover, in cases of myxedema with concomitant hypertension, a drop in diastolic pressure usually occurs following thyroid medication. As a result coronary flow would be decreased and thrombosis formation facilitated.

DYNAMIC CONSIDERATIONS IN MYXEDEMA HEART

In discussing the dynamic events of myxedema heart, it is interesting to compare this type with the circulatory changes that occur in the hyperthyroid heart. Just as hyperthyroidism may cause marked myocardial overactivity, myxedema may on the other hand, produce retarded and sluggish underactivity of the heart muscle. Whereas in hyperthyroidism the prominent signs are tachycardia and loud, vigorous heart sounds, in myxedema, the outstanding signs are bradycardia and faint, feeble heart tones. It has been shown that the velocity of blood flow is reduced in myxedema heart and considerably increased in hyperthyroid heart (Blumgaard, Gargill and Gilligan[23]). Concomitant with a reduced circulatory flow in myxedema there exists a reduced blood volume (Thompson[40]). These probably are a result of depressed metabolic activities. Again, in hyperthyroidism, minute output[23, 40, 41] is augmented while in myxedema it is reduced. A 20

per cent reduction in minute volume occurred in Case 2. It may also be added that in myxedema there is a diminished venous return to the heart as a result of the reduction in the strength of voluntary muscle contraction (Rockwell[43]). In hyperthyroidism venous return is increased.

With this evidence in mind, speculations on the probable mechanism of cardiac dilatation and heart failure in myxedema can be made. It is recognized that a reduced blood volume and diminished circulatory rate with a slow pulse can explain a diminished cardiac output. It may be said that the circulatory load upon the heart in myxedema is actually diminished. These facts cannot in themselves explain the generalized dilatation of the heart which is found in at least 65 per cent of the cases. Then why should the myxedema heart become inefficient? This can best be explained on the ground that the inherent contractility of the myxedema heart is impaired or that the heart succumbs to a state of diminished tonus. In other words, the myxedema heart becomes in all respects a hypodynamic one.[44*] In spite of the decreased load, it becomes weakened to the extent that, in order to do the same amount of mechanical work, it must dilate. To accomplish this, the muscle fibers must lengthen (Starling, and Visscher[45]). Thus the dilatation is a compensatory mechanism on the part of the myocardium in an attempt to maintain normal minute volume. However, when the myxedematous heart dilates to a point beyond which it is no longer able to maintain normal minute volume, systolic discharge is decreased and venous pressure will, in consequence, rise. At this stage the mechanical efficiency of the heart is seriously impaired. We then have the onset of true heart failure. If we accept the idea that the pathological change in myxedema heart is generalized throughout the entire myocardium—a fact which is verified by x-ray and electrocardiographic evidence—then it is not difficult to conceive why all chambers of the heart should become weakened simultaneously. Thus the right heart does not have to wait for the left heart to fail. Hence, the factors which operate to impose right heart failure are facilitated in myxedema heart. Fortunately, were it not for the fact that this mechanism is counterbalanced—at least in the early stages of the disease—by a coexisting lowered blood volume and diminished venous return, it is probable that the incidence of gross congestive failure would be higher.

We can thus summarize the outstanding differences between the hyperthyroid heart and myxedema heart. In the former, because of the direct action of an excess of thyroxin in the heart muscle, the cardiac tone is increased as indicated by increased vigor and loudness of heart sounds with a corresponding increase in heart rate. As a

*The "hypodynamic state" is a term applied by Wiggers[41] to indicate a condition of the heart muscle in which, in spite of increasing venous pressure, systolic discharge is reduced and dilatation of the heart occurs.

rule, there is an increase in systolic pressure. The result is an increased velocity of circulation and an augmented minute volume. However, we cannot consider the hyperthyroid heart as a true hyperdynamic heart (one in which there is increased tonus), because it is possible that the minute volume increase is consequent upon the tachycardia rather than upon the ventricular tonus. On the other hand, the myxedema heart is characterized by a diffuse dilatation of all chambers and by a slow and feeble contraction as indicated by the faint heart sounds. There is eventually a reduction in minute volume accompanied by a diminished velocity of blood flow. The blood pressure as a rule is slightly elevated. This heart is fundamentally hypodynamic in that the working capacity or tonus of the ventricles is reduced, resulting in such a disproportion between diastolic volume and intraventricular pressure increase that for a given pressure rise, there is a much greater increase in volume.

COMMENT

The wide variation in the incidence of congestive failure associated with myxedema as reported by various authors is at the present time impossible to explain. It does not appear to be a matter of improper diagnosis because the concept of gross failure with its objective signs is not only well and uniformly accepted but likewise easily recognized. True enough, the beginning signs of myocardial weakness may be masked to a certain extent by the myxedematous state or the myxedematous condition may in some way interfere with the gross manifestations of an early congestive failure when it would otherwise be apparent. It is also probable that when gross congestive failure appears, it indicates that venous congestion has already progressed to a moderate extent. Other factors that may possibly retard or accentuate the appearance of gross failure are the level of the basal metabolic rate, the degree of secondary anemia, the blood volume, the extent of physical activity participated in by the patient, and the coexistence of coronary disease or hypertension.

When does the true inception of heart failure in myxedema supervene, and what should constitute the criteria by which one can judge the onset of myocardial insufficiency? It is certain that increased venous pressure and decreased minute output with a dilated heart can exist before signs of gross failure in myxedema are evident. Case 2 is a good example of such a situation. It was mentioned previously that this patient's chief complaint was dyspnea. Dyspnea appears to be an outstanding symptom in myxedema. Thus in the series from the Massachusetts General Hospital[20] as previously mentioned, 65 per cent showed dyspnea while only 3 per cent showed gross congestive failure. When a diffusely dilated heart, accompanied by signs of dyspnea, can be demonstrated, then we probably have the existence of early cardiac

failure. This condition was proved to be present in Case 2 when minute volume determinations showed a decreased systolic discharge. Fahr[3] is probably correct when he states that in cases of myxedema which show definite cardiac dilatation, the onset of the condition of heart failure is present. When gross congestive signs will appear, of course, cannot be predicted, but eventually they will manifest themselves. Of the 65 per cent of cases of myxedema which showed definitely dilated hearts, it is very likely that they are the same 65 per cent which showed dyspnea. It would not be surprising, as further studies should show, that a direct correlation will be found to exist in regard to the degree of dilatation, dyspnea and minute output.

It is recognized that conclusions cannot be drawn from the study of this single case. Nevertheless, the suggestion is offered that if more cases are studied from the same angle, much will be learned concerning the problem of heart failure in myxedema.

SUMMARY

The literature on myxedema heart is reviewed and two additional cases are reported. The myxedema heart is unique in the respect that it returns to its normal size after the administration of adequate amounts of thyroid. Upon the withdrawal of thyroid it again dilates and characteristic changes in the electrocardiogram occur. The pathologic physiology of myxedema heart is discussed. Minute volume studies carried out in the case in which dyspnea was the outstanding symptom suggest that myocardial insufficiency may be present even when the gross objective signs of congestive failure are absent. It is assumed, therefore, that when a generalized cardiac dilatation, accompanied by dyspnea, can be demonstrated, congestive heart in myxedema is in all probability present.

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STUDIES IN OSCILLOMETRY*

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OSCILLOMETRY has been in use as a diagnostic method for over fifty years. Recently, however, the French school under the leadership of Vaquez, Gomez, and others, has awakened renewed interest in this subject. Their emphasis has been placed very largely on the height of the oscillometric curve on the one hand, and the recognition of the so-called mean blood pressure on the other.

The method of approach in the studies of which this communication forms a preliminary report, was somewhat different. It concerned itself chiefly with the form of the oscillogram, readings being taken on all extremities in each instance.

METHOD

The Boulitte modification of the Pachon oscillometer has been used for all determinations.

This apparatus has two overlapping, distensible pouches having a combined width of fifteen centimeters. These pouches are enclosed in a rigid web cover fitted with web straps. The apparatus is strapped to the extremity to be studied. By a simple valve arrangement the pouches can be inflated together, or singly.

A manometric dial permits the recording of oscillometric variations at different pressures.

In each case studied, eight oscillograms are made, i.e., of the forearms, upper arms, legs, and thighs on both sides. With the band snugly fitted to the extremity, air is pumped in until the pressure is great enough (in ordinary cases) to prevent any movement of the oscillatory needle. In certain cases even at the pressure of three hundred millimeters of mercury (the limit of the instrument) oscillations still occur. By means of a needle valve, the pressure is dropped ten millimeters at a time, and the height of the oscillation recorded at the various pressures.

Inasmuch as the time element is a factor, the observer announces the oscillations at the various pressure levels, which are then immediately charted by an assistant. By the use of various chart symbols for the different extremities, the four oscillograms for the upper, and again for the lower extremities can be charted on one graph and the two graphs combined on one sheet.

Blood pressure readings are taken by the auscultatory method on the right and left arms as soon as the arm oscillograms are charted. The patient lies recumbent during the test so that the extremities are approximately at the heart level.

Using this technic, several hundred charts were made of patients suffering from diverse conditions, using material from the medical service of the Cincinnati General Hospital.

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OBSERVATIONS

It has become apparent that the height of the oscillometric curve is not greatly influenced by age or sex, provided that the heart is normal and the blood vessels not seriously involved. In all the cases studied, records were made of the physical findings, laboratory findings, electrocardiograms, teleroentgenograms, and other x-ray findings.

The oscillometric index is definitely labile in certain conditions where there is reason to believe that arteriospasm exists. Repeated readings on

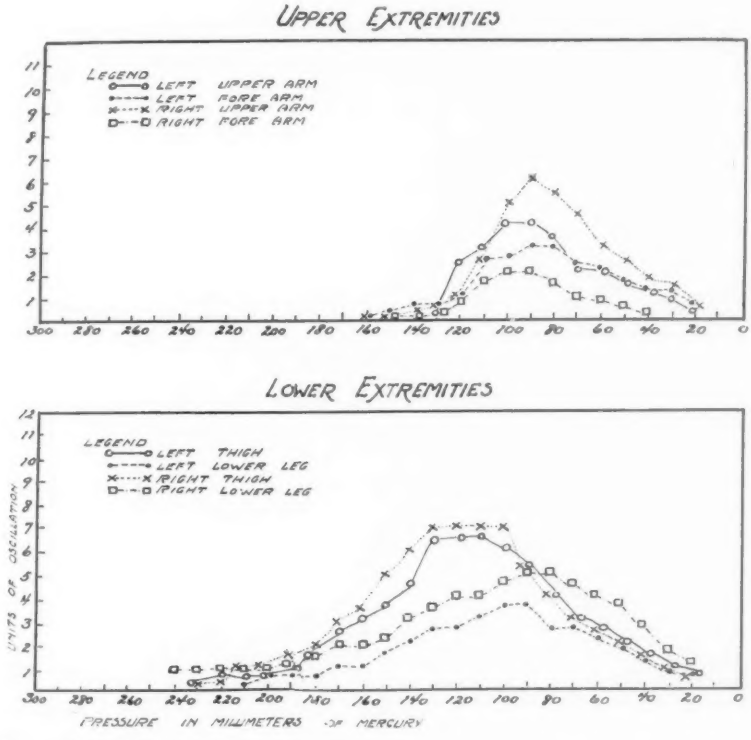

Fig. 1.—Normal oscillogram.

O. P., male, white, aged sixty-five years. Blood pressure 120/60. *Clinical diagnosis:* Pernicious anemia.

the same patient under such conditions will show varying heights of the oscillometric curve.

Experience also demonstrated that the maximal oscillometric phase (MOP) of the brachial oscillogram occurred between 100 and 80 mm. Hg in a great variety of cases, with apparently normal hearts and blood vessels. These findings are in accord with those of Miller and Chester.[1]

The particular point to be emphasized in this preliminary report, is that in oscillometric studies, the form of the oscillogram is of paramount importance.

It would appear that from the type of oscillogram obtained, one may draw certain conclusions as to the condition of the vascular tree in a given case.

Four illustrative oscillograms are presented.

1. The normal oscillogram (Fig. 1) of the upper arm begins to show an oscillometric rise at about 120 mm. Hg and drops to zero between 40 and 30 mm. Hg. Oscillations do occur at higher pressures than 120 mm., but are not marked. The MOP occurs between 100 and 80 mm. Hg.

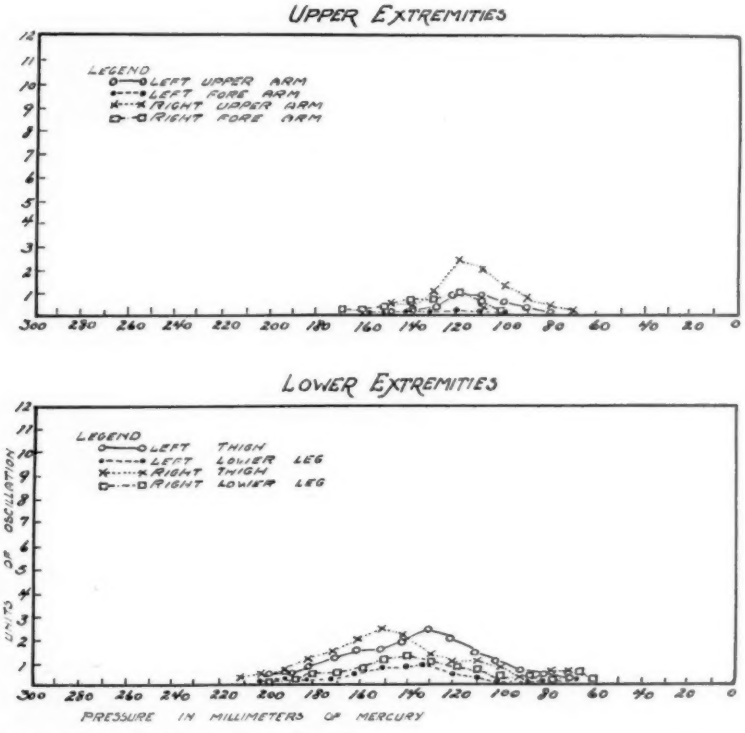

Fig. 2.—Generalized vascular sclerosis.
R. S., male, white, aged forty-nine years. Blood pressure 120/100. *Clinical diagnosis:* Arteriosclerotic heart disease and vascular sclerosis.

The thigh shows oscillations at higher pressures (around 160 mm. Hg), and the drop occurs around 40 mm.

The maximal oscillometric phase shows variations in unit height of oscillations varying from 5 to 6 units on the upper extremity, and up to 7 or 8 units on the thigh.

No conclusion can be drawn from the height of the oscillation as to the actual blood pressure.

2. The oscillogram in marked vascular sclerosis shows a very different picture (Fig. 2).

The oscillations occur over a much narrower range of pressure; the MOP, especially in the lower extremity, is apt to occur at higher pressures—140 to 120 mm. Hg, and the height of oscillation is low, 2 to 3 units.

3. Essential Hypertension.—Here the oscillogram presents a distinct variant from the normal.

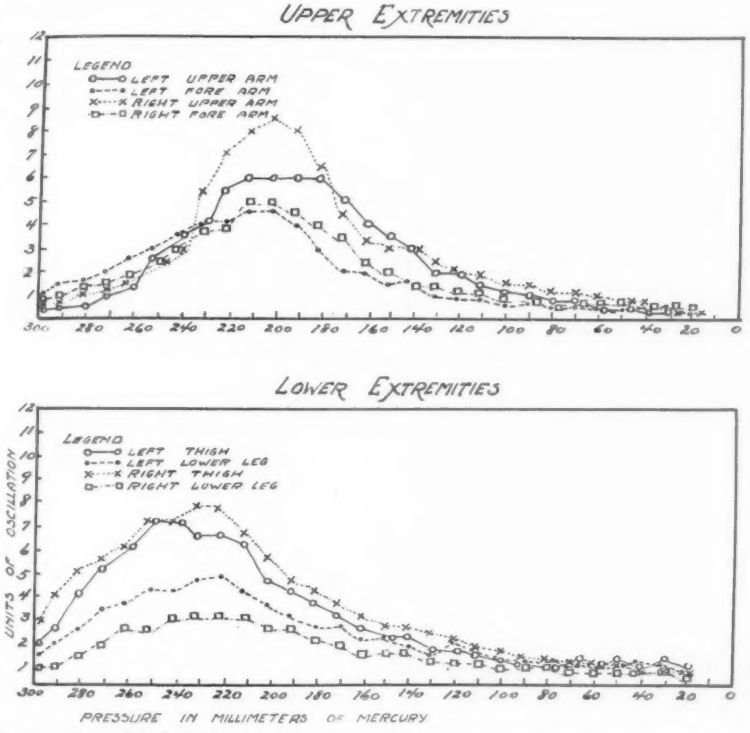

Fig. 3.—Essential hypertension.
E. T., female, white, aged fifty years. Blood pressure 250/160. *Clinical diagnosis:* Essential hypertension and nephrosclerosis.

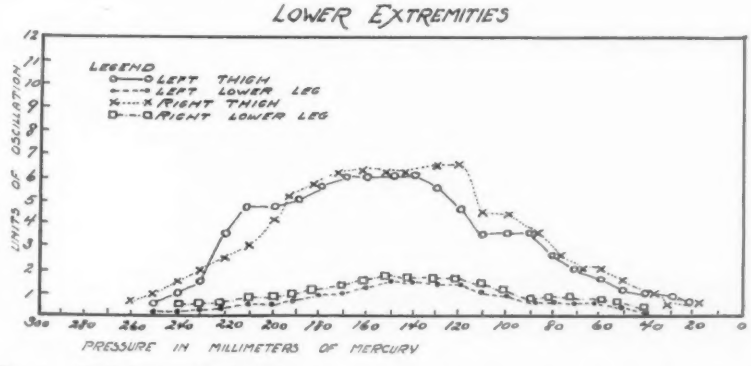

Fig. 4.—Medial arteriosclerosis.
L. L., female, white, aged sixty-eight years. Blood pressure 190/120. *Clinical diagnosis:* Arteriosclerosis. Marked in arteries of lower legs.

There is what might be called a definite shift to the left. In both upper and lower extremities, the MOP occurs at much higher levels (220 to 200 mm. Hg). Oscillations begin at such high pressures as 300 mm. Hg. Thus, as will be noted in Fig. 3, oscillations stood at 3 units at 300 mm. Hg in the right thigh. Furthermore the oscillations approach zero at much higher pressures (around 100 mm. Hg). The unit height of the oscillations is high, 8 to 9, at the MOP.

4. Medial arteriosclerosis (Fig. 4). The striking features of the oscillogram here are, first, the marked difference in the curves of the legs and thighs; second, there is the wide spread of the oscillations beginning around 240 mm. Hg and extending to 40 mm. Hg. The MOP occurs at high level and is often, as in the case illustrated, of the plateau type (170 to 120 mm. Hg).

COMMENT

Too much emphasis must not be laid upon the mere height of the oscillometric curve. In the absence of cardiac hypertrophy and vascular sclerosis, the MOP may show a wide degree of variation in diverse conditions. It even shows great variations in the same patient at different times, depending upon conditions of vasoconstriction, etc. This is well demonstrated in cases of hyperthyroidism without involvement of heart or blood vessels. Allisat[2] also calls attention to this fact.

Oscillograms must be interpreted on the basis of the factors which maintain blood pressure, i.e., the force of the cardiac contraction (the *vis a tergo*), the condition of the blood vessel wall, and the very important factor of peripheral resistance. Whether the fourth factor, blood volume and blood viscosity, is of great importance or not, cannot be decided so definitely at this time.

Samuels[3] in referring to the value of the oscillometer in the study of circulation in the extremities, calls attention to the help given by the oscillometer in differentiating neurogenic from organic arterial disease.

Kramer[4] says that the oscillometer gives information about the deeper vessels which cannot be palpated. It may suggest the occurrence of collateral circulation when definite lesions of the blood vessels are apparent.

Vaquez and his coworkers[5] have stressed the importance of the so-called "mean pressure," as determined by the oscillometer. They conclude that, very often, hypertension is disclosed by elevation of the mean pressure at an earlier age than is shown by elevation of the systolic blood pressure. They apparently pay no attention to the form of the oscillogram.

As one surveys the rather extensive literature on oscillometry which has appeared recently, one is struck by the fact that in nearly all studies, the main emphasis has been placed on the maximal oscillometric phase (MOP). It is the purpose of this communication to call attention to the

much greater importance of the oscillogram itself. From the form of the oscillogram, certain definite deductions may be drawn as to the condition of the vascular tree.

Three typical pathological oscillograms are shown herewith, to demonstrate diverse conditions. It should be added that these types of tracings have been found over and over again, in the several hundred cases studied. The tracings run true to form, so to speak, and it is quite possible to predicate the type of vascular lesion present from the oscillogram itself.

It must, of course, be added that mixed forms occur, as would be expected from the general nature of vascular sclerosis. In such cases definite diagnosis cannot be made from the oscillograms alone.

1. Where the oscillograms of both extremities (upper and lower) are of the low flat type, with oscillations occurring within a comparatively narrow range and with the MOP relatively low (2 to 3 units), there is true arterial thickening, with or without calcification. This condition is well illustrated in Fig. 2. This patient was a white male, aged forty-nine years, with the typical clinical picture of arteriosclerotic heart disease with general vascular sclerosis.

2. The curve in true arterial hypertension without major arterial involvement is characterized by a definite shift to the left. That is, the MOP occurs at high pressure levels, and is itself high. This is well illustrated in Fig. 3, where the MOP occurs at 230 mm. Hg in the lower extremities, and 200 mm. Hg in the upper, with an index of 7 and 8 units respectively. This patient was a white female, aged fifty years, with the clinical picture of hypertension and nephrosclerosis.

3. The curve in hypertensive heart disease with senile arteriosclerosis (Mönckeberg type) is characterized by high thigh curves and low leg curves, or by high curves of one lower extremity and low curves of the other.

In his original communication Mönckeberg[6] in discussing his so-called medial calcification, stressed the fact that medial calcification is much commoner in the extremities than arteriosclerosis. Karsner[7] says that the early change is usually a fatty degeneration of the middle layers of the musculature and elastica of the media, which may be associated with necrosis. The condition is common in old age and affects particularly such arteries as the femoral, radial, temporal, and dorsalis pedis. Severe degrees of peripheral senile sclerosis may be associated with but little sclerosis of the aorta.

Beck[8] reviewed oscillometric curves taken at various levels in cases of thrombo-angiitis obliterans, as well as in cases of peripheral thrombosis and embolism, and compared these readings with those at corresponding levels in the unaffected limb. He found that the oscillometric index at the point just proximal to the point of occlusion, was definitely and consistently larger than the index at the same level in the unaffected limb.

This did not hold good when the lesion was sclerotic in character. In the series of cases studied by the author, this type of curve was found very frequently. The curve shown in Fig. 4, was taken from a white woman aged sixty-eight years with distinct hypertensive heart disease and marked peripheral sclerosis.

SUMMARY

1. The form of the oscillogram, taking curves of all extremities in each case, is of more importance than the estimation of the maximal oscillometric phase.

2. The normal oscillogram may show definite variations in the MOP in the same individual at different times. This is dependent largely upon the condition of peripheral resistance.

3. Typical pathological oscillograms are shown, demonstrating arterial thickening, essential hypertension with nephrosclerosis, and hypertensive heart disease with Mönckeberg arteriosclerosis.

4. From the form of the oscillogram in typical cases definite conclusions may be drawn as to the condition of the vascular tree.

5. Mixed forms of curve are often found. In such cases the oscillogram alone cannot afford definitive diagnosis as to the condition of the vessel walls.

It affords me pleasure to acknowledge a debt of gratitude to Dr. L. G. Herrmann for much constructive criticism and many valuable suggestions given during the course of these studies.

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THE USE OF QUINIDINE IN AMBULATORY PATIENTS FOR THE PREVENTION OF PAROXYSMS OF AURICULAR FLUTTER AND FIBRILLATION; WITH ESPECIAL REFERENCE TO DOSAGE AND THE EFFECTS ON INTRAVENTRICULAR CONDUCTION*

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DETAILED studies on the use of quinidine in auricular flutter and fibrillation have been conducted mainly in cases of the "persistent" forms of these rhythms or during a prolonged attack with the patient at rest and under close supervision. They show that the drug may be relied upon in the majority of suitable cases to abolish auricular flutter or fibrillation and to reestablish a normal rhythm for varying periods of time and with a fair degree of safety. The prevention of attacks in the paroxysmal form of auricular flutter and fibrillation, however, presents somewhat different problems from the practical standpoint, and these may account for the fact that, in general, not quite the same success has been attained in this, as in the treatment during a paroxysm. During the past two years we have followed the clinical course in some detail in twenty-one patients with paroxysmal auricular fibrillation or flutter. These included two cases of active rheumatic carditis, one case of hyperthyroidism, eight cases of arteriosclerosis, two cases presenting no evidence of organic heart disease (Class E), and the remaining ones with heart disease of unknown origin. In several of those who received quinidine in varying doses—in some up to 50 grains daily—the attacks remained uninfluenced; while in a few in whom the attacks appeared to have been diminished in frequency or abolished at one time or another, the influence of the drug could only occasionally be definitely established.

It was a common observation that a dose of quinidine which seemed at one time to render a patient free of attacks, appeared at another time to be without this protective action. This observation, however, may signify any one of a number of different phenomena, such as spontaneous variations in the course of the disease, the development of tolerance to the drug, or extraneous reflexes that may render a circus movement more or less resistant. Under the ordinary conditions of life the patient is subject to widely varying influences—rest, effort, excitement, shock, digestive disorders—all of which are sources of

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metabolic changes or reflex stimuli that may in susceptible individuals serve to start or abolish a circus movement in the auricle. The plan of putting such a patient to bed, establishing the dosage which appears to abolish the attack under these conditions, and then prescribing such doses for long periods of time does not afford an adequate solution of the problem, for the reason that such doses will frequently fail to prevent the recurrence of attacks.

Most of these patients are ambulatory. They may or may not present evidence of organic heart disease. In any case they often complain of little more than these attacks of palpitation and other symptoms such as dyspnea, faintness and weakness attending a paroxysm. Some are entirely without abnormal symptoms during a paroxysm, the presence of the abnormal rhythm being discovered during one of the routine examinations. The incidence, the duration, and the intensity of attacks are likely to vary widely at different times and in different individuals, adding further uncertainties in attempting to assess the usefulness of the drug and to establish suitable dosage for the prevention of attacks.

Among the obstacles in the way of systematic investigation and treatment of these cases with drugs, should be mentioned the lack of continued cooperation on the part of the patient. It is a matter of no difficulty to excite a patient's enthusiasm for a course of quinidine therapy just after a few severe paroxysms that have occurred in a period of a week or two, but it is difficult to sustain his cooperation in the continued daily use of large doses of quinidine for periods of many months in which he is free of attacks. There is a question, indeed, whether such treatment is desirable. The fact is, however, that the use of the drug is interrupted and the attacks recur.

It may be noted that while the control of the paroxysmal forms of auricular flutter and fibrillation presents greater difficulties, the use of quinidine in these cases, has, from one point of view, the advantage of greater safety, even though these patients cannot be subjected to the same degree of supervision as the ones confined to bed. In the paroxysmal forms quinidine may be given in the presence of a normal rhythm to prevent attacks, the only danger being the direct toxic effects of the drug, while in the treatment with quinidine during an attack there are the additional dangers of the very rapid tachycardias in the intermediary stages between the abnormal and the normal rhythm as well as the possibility of the discharge of emboli when the auricles begin to contract after fibrillation has persisted for some time.

One of our cases was extremely favorable for a systematic study; the paroxysms were relatively frequent, they were sufficiently intense to interfere with the patient's occupation, and the intervals between attacks, though very irregular, showed a range sufficiently restricted to afford a basis for comparison. This patient consulted us at the

clinic in August, 1930, because of severe attacks of palpitation during which he was completely incapacitated. They had occurred at frequent intervals during the preceding period of about four years, during which time he had received various forms of treatment but had not obtained any relief. After a considerable interval (before electrocardiograms could be obtained during a paroxysm in order to establish the diagnosis of paroxysmal auricular flutter and fibrillation) treatment with quinidine was started without any interruption of the patient's activities. The result is that, except for intervals during which the drug was withheld for purposes of study, the patient has been virtually free of distressing symptoms for a period which up to the time of writing is about two years.

The observations in this case present several features of special interest with regard to the use of quinidine, more particularly (1) the prolonged administration of extremely large doses of quinidine, (2) the use of quinidine in the presence of intraventricular block, and (3) the almost complete relief of subjective symptoms by a mechanism of quinidine action that does not diminish the frequency but does reduce the intensity of the paroxysms. We report this study in detail together with special observations carried out in ten other patients, bearing on quinidine dosage, the effect of quinidine on intraventricular conduction and the danger of vagal pressure in the presence of a tachycardia.

CASE REPORT

History.—Patient J. B., forty-four years of age, was born in Russia, was married, had three children, and reported good habits. His previous medical and surgical history was negative. He did not smoke. He took tea and coffee in moderation, and no alcohol. He discovered he had heart trouble in 1926 (about six years ago) when he began to be aware of undue shortness of breath and fatigue on effort. About a year later he became subject to attacks of palpitation associated with faintness and weakness. He stated that during these periods the heart "pounded" rapidly and sometimes irregularly. He was usually compelled to interrupt his work during the attacks, although in the intervals he was not seriously troubled with cardiac symptoms and he had no difficulty in continuing with his regular occupation as a tailor. The attacks sometimes appeared while the patient was at rest, although in most instances they seemed to have been brought on by sudden exertion, excitement, fright, eating, or a cold drink. The onset was usually abrupt, the duration variable, and the termination usually abrupt. He had consulted several physicians and had been treated at clinics. For nearly a year up to the time of admission, he had been taking 20 drops of a tincture of digitalis three times daily. From time to time he had received various other medicines including quinidine in small doses. The intensity and severity of the attacks, however, remained uninfluenced.

Physical Examination.—The patient was a healthy looking white male weighing 150 pounds. The significant physical findings were as follows: The heart rate ranged between 60 and 80 per minute and was regular except for occasional ventricular premature beats; the sounds at the base were very distant, and the first sound at the apex was replaced by a systolic murmur not transmitted in any direction; there were no diastolic murmurs. There were no thrills. The left auricle and

ventricle were found considerably enlarged on fluoroscopic examination. The blood count was normal and the blood Wassermann reaction negative. The blood pressure ranged from 118 to 140 systolic, 65 to 90 diastolic. There were no signs of peripheral arteriosclerosis (eye grounds and other peripheral arteries) or peripheral congestion. The electrocardiogram showed a regular sinus rhythm with a bundle-branch block (Fig. 2).

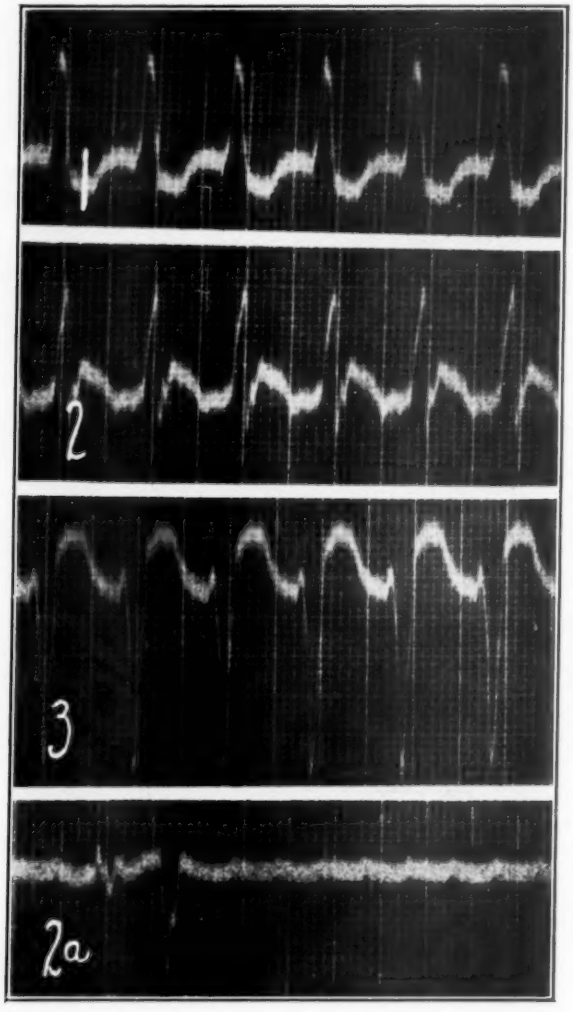

Fig. 1.—Tracing of patient J. B. taken 10/15/30. Auricular flutter with bundle-branch block. Tracing 2 *a* shows ventricular arrest with flutter waves of the auricle during "vagal" pressure.

The diagnosis was heart disease of unknown origin, enlarged heart, normal sinus rhythm, bundle-branch block and slight diminution of functional capacity (Class IIA*). Subsequently there was added to this paroxysmal auricular flutter and fibrillation (Fig. 1).

*Following the nomenclature adopted by the Heart Committee of the New York Tuberculosis and Health Association.

It may be noted that it was about two months after admission to the clinic before an electrocardiogram was obtained during an attack. At this time the heart rate was 150 per minute and regular. Carotid pressure caused complete heart-block with ventricular arrest during which the auricular flutter at 300 per minute could be counted. About three weeks later the patient was again seen during an attack during which the heart rate was also 150 per minute and the rhythm very irregular. Carotid pressure was now without any influence. The tracing taken at this time showed auricular fibrillation.

Incidence and Character of Attacks Before Quinidine.—In some cases of paroxysmal auricular fibrillation and flutter, the attacks are occasionally so mild as to escape the patient's notice, and in these it is difficult to obtain a reliable record of attacks as a basis for a study. As we have already indicated, however, the attacks

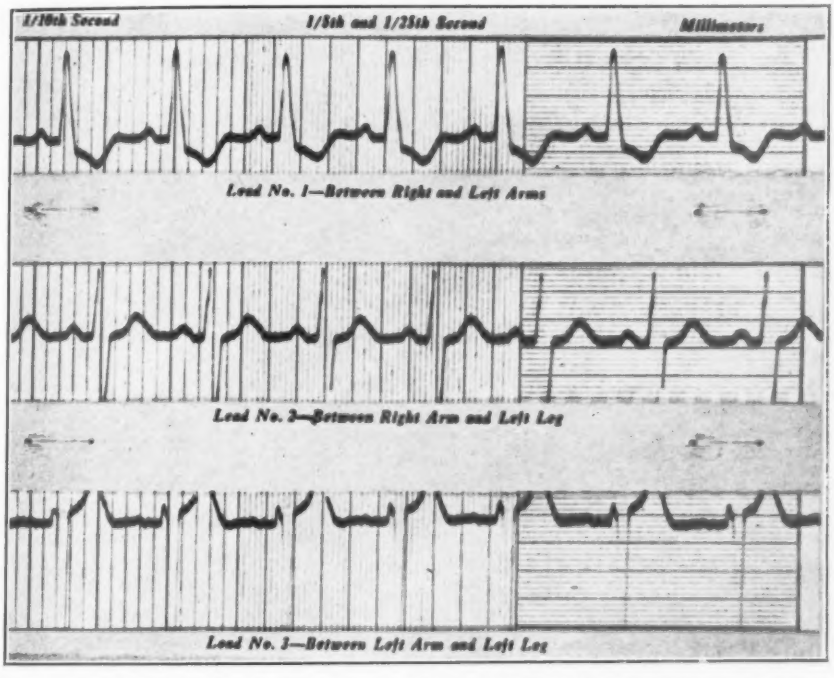
1/10th Second
1/5th and 1/25th Second
Millimeters
Lead No. 1—Between Right and Left Arms
Lead No. 2—Between Right Arm and Left Leg
Lead No. 3—Between Left Arm and Left Leg

Fig. 2.—Tracing of patient J. B. taken 8/18/30 before quinidine was given. The P-R interval is 0.20 and the QRS time is 0.12 second.

of palpitation in this patient were very distressing and interfered seriously with his occupation. These factors helped to insure the patient's complete cooperation in any effort that offered the possibility of relief. Before he came under our observation, he had been instructed by a physician to keep a record of the incidence and duration of attacks as well as of suggestive factors that seemed to him to incite them. This record he brought to us, and together with that made during the control period in our clinic, constitutes a fairly accurate account of the paroxysms during a period of about thirty-one months. These are presented in Table I. An examination of this table shows that before adequate treatment the patient had had 37 attacks of auricular flutter or fibrillation in a period of about thirty-one months. The attacks varied in duration from about one to sixty hours and appeared at intervals varying from five to sixty-six days. At one time there were as many as 3 attacks in a month and at another time two months passed without an attack.

During this entire period of more than two and one-half years, therefore, the patient suffered on the average of one attack in about twenty-five days, lasting on the average about thirteen hours.

TABLE I

INCIDENCE OF ATTACKS BEFORE TREATMENT WITH QUINIDINE IN PATIENT J. B.

DATE	DURATION OF ATTACKS IN HOURS	INTERVALS BETWEEN ATTACKS IN DAYS
4/28/28	48	--
6/ 4/28	13	37
6/28/28	2.5	24
7/12/28	1.5	14
7/19/28	1.5	7
9/ 1/28	3	44
10/10/28	12	39
10/22/28	3	12
12/27/28	3	66
2/14/29	2.5	49
3/31/29	9	45
5/ 1/29	7.5	31
5/21/29	60	21
7/ 6/29	1	46
8/24/29	6	49
9/27/29	16.5	34
10/10/29	6.5	13
11/ 6/29	13	27
12/18/29	8	42
1/ 9/30	3	22
1/18/30	2	9
1/23/30	17.5	5
1/29/30	18	6
3/29/30	12	59
4/ 7/30	4	9
4/16/30	5	9
5/12/30	3	26
5/26/30	12	14
6/ 3/30	24	8
6/30/30	4	27
7/14/30	15	14
8/ 5/30	50	22
8/28/30	23	23
9/25/30	30	28
10/15/30	23	20
10/30/30	15	15
11/21/30	17	22

Incidence and Character of Attacks During Treatment With Quinidine.—A similar record was obtained during the period of treatment with quinidine. The facts are tabulated in Table II, which includes in addition the results of all the clinical examinations of the heart and analyses of the electrocardiograms.

Treatment was started with a daily dose of 12 grains of quinidine sulphate (6 grains twice daily) which was continued over a total period of twenty-eight days. During this time the patient had two severe attacks similar to the previous ones.

The dose was increased to 30 grains daily (10 grains three times daily) and in a period of six days there were 4 attacks of palpitation. This was the first time that the attacks had ever occurred with such frequency. It was, however, also the first time that the attacks were so "mild," producing only a slight sense of irregular palpitation during which the patient continued his work without serious discomfort.

The dose was increased to 40 grains daily (10 grains every four hours). In this period there was an almost continuous attack of mild palpitation which hardly disturbed the patient at all, and which lasted during the seven days in which this dose was taken and during the succeeding seven days in which a dose of 50 grains daily (10 grains every three hours) was taken. This attack was not absolutely continuous, but the interruptions in the abnormal rhythm in this period of two weeks were of very brief duration. The electrocardiograms taken during these attacks which the patient described as almost negligible showed auricular fibrillation with relatively slow ventricular rates of from 70 to 92 per minute as compared with the rate of 150 per minute seen before the quinidine.

The dose was then increased to 60 grains daily (10 grains every two hours) and during the total period of twenty-eight days in which this dose was taken there were four attacks which were again so mild as to be practically negligible in the mind of the patient. At times the sense of palpitation and irregular heart action was so slight as to make it difficult for him to be certain as to the time of onset and disappearance of the attacks.

Maximum Tolerance.—Inasmuch as attacks still occurred at this level, the dosage was increased to 70 grains daily and during the next two weeks there were no attacks, although the period is too short to ascertain whether attacks were possible at this level of dosage. There appeared, however, some blurring of vision and impaired hearing, and after two weeks these doses were discontinued. This procedure showed, therefore, that at one period at least, in this patient, the doses of quinidine which failed to prevent attacks of paroxysmal flutter or fibrillation completely were very near to the largest doses that could be tolerated without extracardial toxic symptoms.

Prolonged Effects.—In the subsequent course, as seen in Table II, an attempt was made to ascertain whether some lasting effect might not result from the prolonged treatment with quinidine in such a case, so that smaller doses would maintain the status established by the large ones. During this test only two paroxysms occurred in a total period of 213 days after daily doses varying from 20 to 50 grains. This is considerably longer than the longest intervals between attacks before the use of quinidine. However, since this status could not be maintained subsequently by similar doses, the significance of this observation remains uncertain. That there is some lasting effect after prolonged treatment was shown during the period of the larger doses. A dose of 60 grains daily was taken continuously, up to the time of writing, for 364 days. This appeared to be the optimum daily dosage in this patient, because at this level of dosage the paroxysms were milder and less frequent than with the smaller doses. The continued use of this dosage has given a much longer period (nearly one year) of freedom from paroxysms than at any time during the control.

As already indicated, during the early period of about fifteen months in which the larger doses of quinidine were used, the patient regarded himself as almost "cured." There was not a single attack sufficiently severe to make it necessary for him to discontinue his work, although this was necessary during practically every attack before the quinidine therapy. The attacks which now occurred were so mild and disturbed the patient so little that their frequency was for a time lost sight of and the impression gained hold in the clinic that this was a patient whom quinidine had rendered almost free of paroxysms of auricular flutter and fibrillation. We were, therefore, surprised to discover upon careful analysis of the data that not only was the patient not rendered free of attacks during that period, but that on the contrary, their frequency had actually increased. Leaving out of consideration the almost continuous attack lasting two weeks during the early stages

TABLE II

INCIDENCE OF ATTACKS DURING TREATMENT WITH QUINIDINE IN PATIENT J. B.

DATE	DAILY DOSE OF QUINIDINE IN GR.	TOTAL CONTINUOUS PERIOD OF GIVEN DOSE IN DAYS	DURATION AND SEVERITY OF ATTACKS IN HOURS	INTERVAL BETWEEN ATTACKS IN DAYS	RHYTHM	RATE	P-R	QRS
8/11/30	0	--	--	--	NSR, VPC	60	--	--
8/18/30	0	--	--	--	NSR, VPC	80	0.20	0.12
8/25/30	0	--	--	--	NSR, VPC	72	--	--
8/28/30	0	--	23, severe	23	--	--	--	--
9/ 8/30	0	--	--	--	NSR, VPC	68	--	--
9/25/30	0	--	30, severe	28	--	--	--	--
9/29/30	0	--	--	--	NSR, VPC	92	--	--
10/15/30	0	--	23, severe	20	A. Flutter	A300 V150	--	0.12
10/20/30	0	--	--	--	NSR, VPC	65	--	--
10/30/30	0	--	15, severe	15	A. Flutter	A300 V150	--	--
11/ 3/30	0	--	--	--	NSR, VPC	76	--	--
11/21/30	0	--	17, severe	22	A. Fibrill.	150	--	0.12
11/24/30	0	--	--	--	NSR, VPC	64	--	--
12/ 8/30	12	14	--	--	NSR, VPC	64	--	--
12/17/30	12	23	12, severe	26	--	--	--	--
12/20/30	12	26	49, severe	3	A. Fibrill.	130	--	0.12
12/22/30	12	28	--	--	NSR, VPC	78	--	--
12/25/30	30	2	7, mild	3	--	--	--	--
12/27/30	30	4	12, mild	2	--	--	--	--
12/28/30	30	5	7, mild	1	--	--	--	--
12/29/30	30	6	5+, mild	1	A. Fibrill.	90	--	0.15
12/30/30	40	1	12+, mild	1	--	--	--	--
1/ 5/31	40	7	almost constant	--	A. Fibrill.	88	--	0.15
1/12/31	50	7	almost constant	--	A. Fibrill.	92	--	0.17
1/19/31	50	14	mild	6	A. Fibrill.	70	--	0.17
1/21/31	60	2	brief, mild	2	--	--	--	--
1/22/31	60	3	brief, mild	1	--	--	--	--
1/26/31	60	7	--	--	NSR	70	0.24	0.16
1/29/31	60	10	15 min., mild	7				
2/ 2/31	60	14	--	--	NSR	64	--	--
2/ 6/31	60	18	10, mild	8	NSR	60	--	--
2/16/31	60	28	--	--	NSR	60	0.24	0.14
3/ 2/31	70	14	--	--	NSR	56	--	--
3/ 4/31	0	2	18, mild	26	--	--	--	--
3/ 7/31	0	5	18, mild	3	--	--	--	--
3/ 9/31	0	7	--	--	NSR	60	--	--
3/23/31	50	14	--	--	NSR	62	--	--
4/ 6/31	50	28	--	--	NSR	60	0.23	0.13
4/15/31	40	9	brief, mild	39	--	--	--	--
4/17/31	40	11	brief, mild	2	--	--	--	--
4/20/31	40	14	--	--	NSR	63	--	--
5/ 4/31	50	14	--	--	NSR	72	--	--
5/18/31	50	28	--	--	NSR	72	--	--
6/15/31	50	56	--	--	NSR	70	--	--
7/13/31	40	28	--	--	NSR	60	0.20	0.13
8/ 1/31	20	19	18, severe	106	--	--	--	--
8/10/31	20	29	--	--	NSR	70	0.20	0.12
9/28/31	30	49	--	--	NSR	60	--	--

TABLE II—CONT'D

DATE	DAILY DOSE OF QUINIDINE IN GR.	TOTAL CONTINUOUS PERIOD OF GIVEN DOSE IN DAYS	DURATION AND SEVERITY OF ATTACKS IN HOURS	INTERVAL BETWEEN ATTACKS IN DAYS	RHYTHM	RATE	P-R	QRS
10/19/31	20	21	--	--	NSR	60	--	--
11/ 2/31	20	35	--	--	NSR	70	0.20	0.12
11/16/31	10	14	5, mild	107	NSR	80	0.20	0.12
12/ 1/31	20	15	24, severe	15	--	--	--	--
12/ 7/31	20	21	8, mild	6	--	--	--	--
12/14/31	20	28	--	--	NSR	68	--	--
12/28/31	30	14	6, 15, 3½, mild	3 in 2 wk.	NSR	70	0.20	0.12
1/11/32	40	14	mild, brief	14?	NSR	64	--	--
1/22/32	50	11	brief, mild	11?	--	--	--	--
1/25/32	50	14	--	--	NSR	68	--	--
1/29/32	50	18	brief, mild	7?	--	--	--	--
2/15/32	50	35	--	--	NSR	70	0.20	0.13
2/29/32	60	14	brief, mild	3 in 2 wk.	NSR	60	--	--
3/28/32	60	42	brief, mild	--	NSR	68	--	--
4/11/32	60	56	--	--	NSR	65	0.24	0.15
5/ 2/32	60	77	--	--	NSR	60	0.24	0.16
5/16/32	60	91	--	--	NSR	60	0.24	0.16
5/23/32	60	98	--	--	NSR	60	0.24	0.16
6/ 6/32	60	112	--	--	NSR	60	0.18	0.15
6/27/32	60	133	--	--	NSR	60	0.24	0.16
7/18/32	60	154	--	--	NSR	70	0.24	0.16
8/29/32	60	196	--	--	NSR	60	0.24	0.15
9/26/32	60	224	--	--	NSR	62	--	--
10/24/32	60	252	--	--	NSR	60	0.24	0.16
12/19/32	60	308	--	--	NSR	64	0.24	0.16
2/13/33	60*	364	--	--	NSR	60	0.24	0.16

NSR (Normal sinus rhythm); VPC (ventricular premature contractions).

*A daily dose of 70 grains was taken for one week during this period to determine the development of tolerance to quinidine.

(?) Indicates that the exact interval could not be established in these cases.

of the quinidine therapy, there occurred at least 30 attacks in about fifteen months, or, on the average, at least one attack in about fifteen days in this period, as compared with one in about twenty-five days during the time before the quinidine therapy, and such frequency as five attacks in one week had never been approached in the entire control period of over two and a half years.

An examination of the clinical records and the electrocardiograms taken during the period of quinidine therapy shows that starting at the level of 30 grains daily, ventricular premature contractions disappeared. During the period of auricular fibrillation there was in evidence, at this level of dosage, depression of both A-V conduction and intraventricular conduction, the ventricular rate having slowed from one of 150 to about 90 per minute, and the QRS time having increased from 0.12 to 0.15;* the maximum QRS time of 0.17 second appeared at the level of dosage of 50 grains.

*The figures for P-R and QRS intervals represent the average of ten readings in every instance.

The normal sinus rate was not slowed by any doses of quinidine, although there was a tendency to moderate bradycardia during the control period. During the periods of normal sinus rhythm, A-V conduction was found impaired only during the level of dosage of 50 to 60 grains, the normal P-R interval of 0.20 second increasing to 0.24 second. Simultaneously intraventricular conduction was usually impaired, the QRS time increasing from 0.12 to 0.16 second.

DISCUSSION

Mechanism of Action.—In the foregoing case the use of large doses of quinidine resulted in marked relief of symptoms. There were two different mechanisms, however, by which this was obtained. While after prolonged treatment paroxysms appeared to have been completely abolished, in the first period of about one year almost complete relief of subjective symptoms was obtained at a time when contrary to expectations the frequency of paroxysms had not diminished but markedly increased.

In the presence of auricular fibrillation quinidine frequently at first accelerates the ventricular rate owing to depression of the vagi.[1] Quinidine may, however, depress A-V conduction by a direct action of the drug upon the conduction tissues.[1] Usually this latter action does not play an important rôle in the therapeutic effects of the drug in auricular flutter or fibrillation. In this case, however, the beneficial effects of quinidine for about fifteen months were expressed almost entirely by this action on A-V conduction. Whereas the ventricular rate ranged around 150 during the attacks of fibrillation before the quinidine therapy, they now ranged around 80 to 90 per minute. The maximum effect on the ventricular rate resulted from a daily dose of quinidine which increased the P-R interval during the normal sinus rhythm by 0.04 second, although marked interference with passage of impulses from the fibrillating auricles to the ventricles occurred during a much lower level of dosage (30 grains daily) which was insufficient in this patient to produce any change in the P-R interval during the normal sinus rhythm.

Before ascribing the greater frequency of the paroxysms to a direct action of quinidine, it was necessary to take into consideration the fact that as the patient improves he is very likely (though he denied it) to permit himself more frequent exposure to influences that provoke attacks, such as excitement and indiscretion in diet. This did not appear to play any part in this case because, as seen in Table II, 5 attacks occurred in the first week in which the larger doses were used. The greater frequency of the attacks appears, therefore, to be due to a direct action of the drug, and while quinidine usually renders the auricles unfavorable for fibrillation or flutter, in this case during one period the opposite occurred.

Lewis and his coworkers[1] showed that quinidine may exert two antagonistic effects in the auricle, lengthening the refractory time which

would tend to abolish the circus movement, and slowing of the speed of conduction which would tend to prevent its cessation. A relative preponderance of this latter action in our patient would explain the observation in the early period of the quinidine therapy that paroxysms of fibrillation occurred more frequently and that one attack persisted almost continuously for two weeks, although not one paroxysm in a period of more than four years had ever lasted as long as three days. With the larger doses of 60 grains daily, however, sufficient increase in the refractory time probably occurred to render the auricle

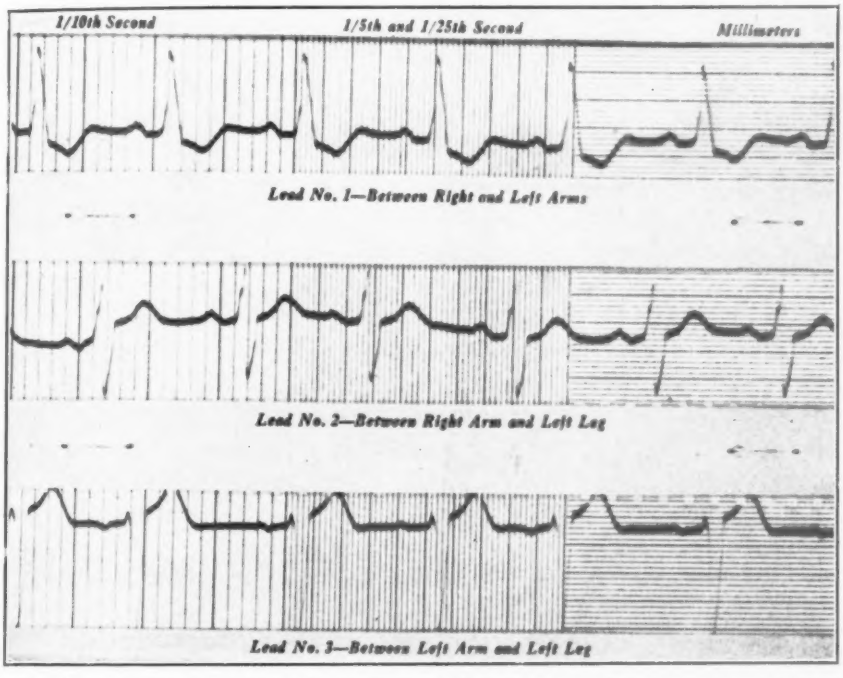
1/10th Second
1/5th and 1/25th Second
Millimeters
Lead No. 1—Between Right and Left Arms
Lead No. 2—Between Right Arm and Left Leg
Lead No. 3—Between Left Arm and Left Leg

Fig. 3.—Tracing of patient J. B. taken 8/29/32 after a daily dose of 60 grains of quinidine sulphate for a period of twenty-eight weeks. The P-R interval is 0.24 second and the QRS time is approximately 0.16 second.

less favorable for fibrillation or flutter because during this level of dosage, the attacks were of very brief duration and subsequently completely disappeared.

Quinidine in the Presence of Bundle-Branch Block.—Quinidine depresses intraventricular conduction,[2] and under some conditions bundle-branch block believed to be due to quinidine has been reported.[3, 4] Wilson and Wishardt[5] reported a case of fatal poisoning with quinidine in which the electrocardiogram showed progressive spreading of the QRS group until the normal contour of the ventricular deflections was lost. The presence of bundle-branch block in our case presented, therefore, a theoretical contraindication to the use of large doses of quinidine. However, doses up to 30 grains daily dur-

ing the period of normal sinus rhythm produced no change in the QRS time, while doses of 60 grains produced a prolongation of the intraventricular conduction time by about 30 per cent (Fig. 3). With a fixed dosage, this effect was not progressive and promptly disappeared when the dose was diminished. Viko, Marvin and White[4] did not observe any prolongation of the QRS time during quinidine therapy (dosage not stated) in 3 patients who had bundle-branch block at the start. We administered quinidine to 8 patients with normal sinus rhythm, whose tracings showed a normal QRS time, and found that daily doses of 30 grains increased the QRS time by 33 per cent in one case, and daily doses of 50 grains increased the QRS time by 20 per cent in another case. It may be fairly assumed, therefore, that in the presence of bundle-branch block intraventricular conduction does not necessarily show any unusual susceptibility to depression by quinidine. It would be well, however, in view of the possibility of producing serious impairment of intraventricular conduction with large doses of quinidine, in any case, even in the presence of a normal QRS time, to control the gradual increase in dosage, as in this patient, by frequent electrocardiograms.

Vagal Pressure.—We have already referred to the influence of vagal pressure in this patient during an attack of flutter. Vagal pressure has been used in experimental studies[6, 7] and is commonly employed for various diagnostic purposes, especially for differentiating types of tachycardias. It is well known that in auricular flutter vagal pressure frequently causes the ventricular rate momentarily to diminish to one-half by the production of a greater degree of A-V block. Such an effect helps to distinguish this from auricular paroxysmal tachycardia, in which the same procedure may cause complete disappearance of the ectopic rhythm. In cases in which pressure over the carotid sheath fails, other procedures such as a deep inspiration or pressure on the eyeballs will frequently produce a similar change in the ventricular rate. The diagnosis is sometimes uncertain without this test. For example, in the case of patient J. B., it was only in the period of ventricular arrest produced by vagal pressure that the deflections of auricular flutter could be seen (Fig. 1). During the vagal pressure lasting 16 seconds, however, alarming symptoms occurred; there was a sensation of heat, followed by marked pallor and almost complete loss of consciousness. In the presence of a fatigued A-V conduction, the vagal pressure caused complete block lasting 16.4 seconds, with ventricular arrest during the first 5.5 seconds, and only 7 escaped idioventricular beats appeared during the entire period of 16.4 seconds. This was followed by a prolonged period of auricular flutter with an irregular ventricular response. Fairly long periods of cardiac arrest following vagal pressure have been reported by others.

Nathanson[8] recently described a case in which cardiac standstill for a period of 7.2 seconds occurred in an old patient with a sinus rhythm after right vagal pressure. Although in our experience, as well as in that of others, vagal pressure has proved to be a relatively safe procedure, it needs hardly to be mentioned that such sudden and marked fluctuations in heart rate as occurred in our patient, from 150 to 30 per minute, are to be avoided.

From time to time, attention has also been called to alarming symptoms that occasionally appear as a result of vagal pressure.[7] This was

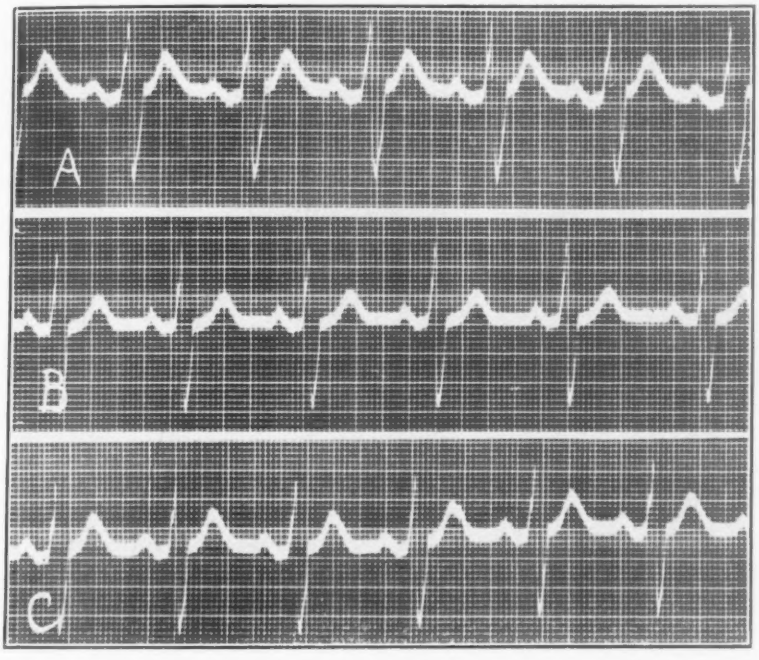

Fig. 4.—Tracings of patient J. B., Lead II only, showing the rapid recovery from the effects of quinidine. *A*, Taken 5/24/32, after 60 grains quinidine sulphate daily for ninety-nine days, shows P-R interval of 0.250 second and QRS time of 0.164 second; *B*, taken 5/25/32, after quinidine was withheld for twenty-four hours, shows P-R interval of 0.220 second and QRS time of 0.139 second; *C*, taken 5/26/32, after 60 grains quinidine sulphate in twenty-four hours, shows P.R. interval of 0.230 second and QRS time of 0.158 second.

shown by another case of auricular flutter which came to our attention* and in which additional observations also illustrate in a striking manner the effect of a tachycardia on ventricular automaticity.

This patient, a male, aged sixty-two years, had arteriosclerotic heart disease and a moderate degree of functional limitation. His blood pressure was 130/70 mm. He was admitted to the hospital during an attack of auricular flutter in which the electrocardiogram showed an auricular rate of 320 and the ventricular beat was practically regular at a rate of 150 per minute. On some days the ventricular beat was found to be irregular and slow due to flutter with varying A-V block. Right

*This patient was seen by one of us (H. G.) on the Second (Cornell) Medical Division of Bellevue Hospital through the courtesy of Dr. Ephraim Shorr.

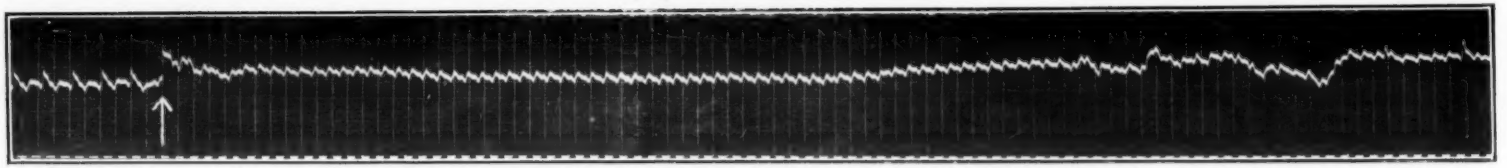

Fig. 5.—Tracing of patient with auricular flutter in whom "vagal" pressure produced ventricular arrest for 15.4 seconds resulting in a convulsion. The arrow indicates the point at which "vagal" pressure was applied.

vagal pressure was applied several times during the course of this attack. In each case the vagal pressure resulted in ventricular arrest, and the pressure was continued until ventricular action was resumed or alarming symptoms appeared. At one time (May 23, 1932) when the ventricular rate was slow (80 per minute) due to flutter with irregular block, vagal pressure resulted in complete ventricular arrest for only 6.8 seconds. At another time (May 20, 1932) when the ventricular rate was rapid (150 per minute), vagal pressure resulted in complete ventricular arrest for much longer periods of time—9.8 seconds (in the test performed in the morning), and 15.4 seconds (in the test performed in the afternoon). The latter pause resulted in a convulsion. The long duration of this period of ventricular standstill as the result of vagal pressure is unusual. The tracing is reproduced in Fig. 5.

We have stressed the danger of vagal pressure in connection with these cases because rapid excitation of the ventricle (as by an auricular flutter) tends to depress its automaticity,[9, 10] and, therefore, the production of complete heart-block by vagal pressure during a tachycardia is particularly liable to result in prolonged arrest of the ventricle. In the diagnostic use of this test it would diminish the risk by applying the vagal pressure only momentarily.

Dosage.—Although the average dose of quinidine in the treatment of auricular fibrillation is from about 15 to 30 grains daily, there are several reports on the use of extremely large doses. Viko, Marvin and White[4] gave daily doses up to 60 grains. Levine and Fulton[11] gave as much as 112 grains in twenty-four hours to one patient with ventricular tachycardia, and 36 grains daily for months to another. In our patient the dosage was gradually increased to the point of minor toxic effects. Altogether he consumed a total of 38,456 grains (more than 75 ounces of quinidine sulphate) or an average of about 48 grains daily for 802 days. It is well to note, however, that a daily dose of quinidine probably exerts its maximum action in the first few days and that practically no appreciable cumulation, in terms of effects, is in evidence when this dose is continued for months. There are several experimental studies which show that quinidine is very rapidly excreted.[12, 13] In the present case when 70 grains of quinidine were given daily, visual and auditory disturbances occurred after the first day, continued in about the same intensity during the two weeks, and disappeared the day following the withdrawal of the drug. The continued use of a daily dose of 60 grains over a period of one year did not show enough cumulation to give as marked effects as 70 grains daily given for one day.

Inasmuch as the development of tolerance to the drug during prolonged administration would vitiate the significance of the absence of subjective symptoms as an indication of the absence of cumulation, the dose was increased to 70 grains daily for one week, after 60 grains daily had been taken for almost one year. The results show that appreciable tolerance had apparently not developed because during this test ringing in the ears and mild deafness appeared, as it did during similar dosage in the early part of the study.

Interesting observations also bearing on this point were made in this patient using conduction changes as criteria of quinidine action (Fig. 4). After a daily dose of 60 grains for about three months, the tracing (tracing A) taken two hours after the last dose of 10 grains, showed a P-R interval of 0.250 second as against the control of 0.20 second, and a QRS time of 0.164 second as against 0.12 second in the control. Marked recovery was in evidence twenty-four hours after the drug was discontinued, the tracing then showing a P-R interval of 0.22 second and a QRS time of 0.139 second (tracing B). The drug was then administered for one day, and 60 grains (tracing again taken two hours after the last dose of 10 grains) produced almost the full effect upon the QRS time that was maintained by that daily dosage for months, namely, QRS time of 0.158 second (tracing C). The P-R interval after this dose was 0.233 second showing that in this case it required more than one daily dose to produce the full effect on A-V conduction. However, after a daily dose of 60 grains for one week, the P-R interval was found prolonged by about 20 per cent beyond the control and the QRS time by about 30 per cent, and the continued use of such dosage for about twelve months did not produce any greater effect.

One frequently finds in the literature that the doses of quinidine necessary to reestablish a normal rhythm are expressed in terms of total quantities.[3] From the foregoing it is clear, however, that the fact of importance in the matter of dosage of quinidine, from the standpoint of the therapeutic effects,* but more especially of toxic effects, is the *size of the daily dose rather than the length of time such doses are continued*, or the total quantity taken over a period of time, and that in the case of a dose which has not caused toxic effects in the first few days, it is unlikely that toxic cardiac effects from the direct action of the drug will result from its continued administration for long periods of time. It may be well to state that emphasis should be placed, in this connection, on the toxic *cardiac* effects, because, as has been shown by Gold and Modell,[2] the elimination of quinidine from cardiac structures is apparently faster than from other structures—for example, the central nervous system—so that repeated doses of quinidine which may give no indication of cumulation in the changes produced in the electrocardiogram, may, if large enough, show sufficient cumulation to produce toxic effects by action upon the central nervous system.

We have already referred to several factors which appear to influence the size of the daily dosage of quinidine in the ambulatory patient. A series of observations carried out in another patient are of importance in this connection and may be reviewed briefly.

*Therapeutic effects are sometimes seen only after the repetition of a fixed daily dose for several days, but this is apparently due mainly to a changing susceptibility of the abnormal mechanism rather than to cumulation of the drug.

This patient, M. K., aged twenty-six years, had rheumatic heart disease with mitral insufficiency and enlarged heart. There was no impairment in functional capacity. During the past two years he had been subject to attacks of paroxysmal auricular fibrillation and flutter (rate of the flutter varying from 210 to 300 per minute). Because of the rheumatic infection his A-V conduction was frequently found prolonged, the tracing showing P-R intervals as high as 0.26 second and dropped beats. This probably accounted for the fact that the ventricular rates during the periods of fibrillation and flutter were only occasionally faster than 100 per minute. He was given quinidine and the dosage was gradually increased until he received 50 grains daily (10 grains at approximately three-hour intervals). Larger doses exceeded his tolerance and produced toxic symptoms (dizziness, mild deafness and ringing in the ears) so that it was not possible to ascertain whether they would prevent the paroxysms.

An effort was made to establish the single dose of quinidine which during auricular flutter would reestablish a sinus rhythm in this patient. During the visit to the clinic a tracing was taken, and when flutter was present a dose of 10 grains of quinidine sulphate was given by mouth. The patient then rested quietly and additional tracings were taken at hourly intervals. This dose sufficed to reestablish a sinus rhythm within one to two hours in four out of five such tests carried out during a period of six weeks. The effect appeared in approximately the time required for the production of the maximum effects of a dose of quinidine as observed by others.[14] Yet in a period of sixteen months (including the above mentioned six weeks), auricular flutter prevailed when the patient appeared at the clinic during fourteen of seventeen visits, although he was taking 30 to 50 grains of quinidine sulphate daily, divided into capsules of 10 grains each at approximately four-hour intervals, the last dose being taken approximately two hours before the examination. A rest period in the clinic during five of these sessions, similar to that during the special tests, did not establish a normal rhythm.

This illustrates, therefore, that while during rest this patient was fairly susceptible to quinidine, so that a single dose of 10 grains sufficed to abolish flutter and reestablish a normal rhythm, under the ordinary conditions of activity he appeared so resistant that doses up to 50 grains daily were insufficient to keep him free of paroxysms.

It is common practice to prescribe small maintenance doses of quinidine (usually of the order of about 6 grains daily) to prevent relapse to fibrillation after a normal sinus rhythm has been established by large doses. There is as yet no sufficient proof that such a plan of dosage plays any material rôle in the persistence of the normal rhythm. Viko, Marvin and White[4] found that relapses to fibrillation occurred in as many patients who received continued "maintenance" doses of quinidine as in those in whom quinidine was discontinued after the normal rhythm was established, although the dissimilarity between some aspects of the two groups led them to the view that the "maintenance" dose did exert some influence. Our own experience leads us to the belief that the routine use of the smaller maintenance doses of quinidine to prevent the recurrence of flutter or fibrillation in the ambulatory patient is probably not sound, and that in general more intense quinidine effects are necessary to overcome the influences in the ambulatory patient that tend to precipitate an at-

tack of fibrillation or flutter than those necessary to abolish an attack in the patient that is confined to bed. Indeed the necessary intensity of quinidine effects may even exceed the patient's tolerance for the drug so that it becomes impossible to prevent attacks while the patient is up and about, as in the case (patient M. K.) just cited. To what proportion of cases the foregoing observations are applicable remains to be determined by more intensive study of larger numbers of ambulatory patients with paroxysmal auricular fibrillation and flutter.

SUMMARY AND CONCLUSIONS

1. In the way in which quinidine has been employed up to the present time, it has not proved so useful for the prevention of paroxysmal attacks of auricular flutter and fibrillation in the ambulatory patient as for the abolition of such attacks in the patient confined to bed. Some of the reasons for this are discussed.

2. It is indicated that there is less danger in the use of quinidine in patients with paroxysmal auricular fibrillation and flutter to prevent attacks than to abolish the abnormal rhythm during a paroxysm.

3. Although quinidine depresses intraventricular conduction (prolongs QRS time) the presence of bundle-branch block due to heart disease does not indicate necessarily any undue susceptibility to this action of quinidine.

4. Illustrations are cited of the value and dangers of "vagal" pressure during a tachycardia. Because rapid excitation of the ventricle is liable to impair its automaticity, "vagal" pressure in auricular flutter may, by producing complete heart-block, cause prolonged arrest of the ventricle with alarming symptoms.

5. Depression of A-V conduction by quinidine usually does not play an important rôle in the therapeutic effects of the drug in auricular flutter and fibrillation. However, in one case which we report, depression of A-V conduction by very large doses of quinidine was solely responsible for the almost complete symptomatic relief during a period of more than a year. Another unusual aspect of the action of quinidine in this patient was the fact that the frequency of the paroxysms of fibrillation or flutter were not diminished but were nearly doubled during this period. The probable mechanism of this unusual reaction to quinidine is discussed.

6. A fixed daily dose of quinidine produces its full effects very early, so that if it has not produced toxic effects in the first few days, it is unlikely that toxic effects from the direct action of the drug will result from its continued administration for long periods of time. Thus in one of our patients a daily dose of 60 grains of quinidine sulphate prolonged the A-V conduction time by 20 per cent and the

intraventricular conduction time by 30 per cent after the first few days, but the continued use of this dose for 364 days did not increase these effects further.

7. Since quinidine is rapidly excreted and shows very slight "cumulation," the matter of importance in dosage is the size of the daily dose rather than the total quantity given over a period of time.

8. Evidence is presented in support of the view that the use of a small "maintenance dose" of quinidine to maintain the normal rhythm established with larger doses, exerts no appreciable influence on the persistence of the normal rhythm in the ambulatory patient, and that in general more intense quinidine effects are necessary to overcome the influences that precipitate an attack of flutter or fibrillation in the ambulatory patient than to abolish an attack while the patient is at rest.

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THE IDENTIFICATION OF THE SEPARATE COMPONENTS OF THE QRS COMPLEX

With Special Reference to the So-called Prominent Q-Wave in Lead III

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THE separate components of the QRS complex in the electrocardiogram are not commonly identified in routine clinical practice. Since the appearance of the "prominent Q_3" as a new sign on the diagnostic

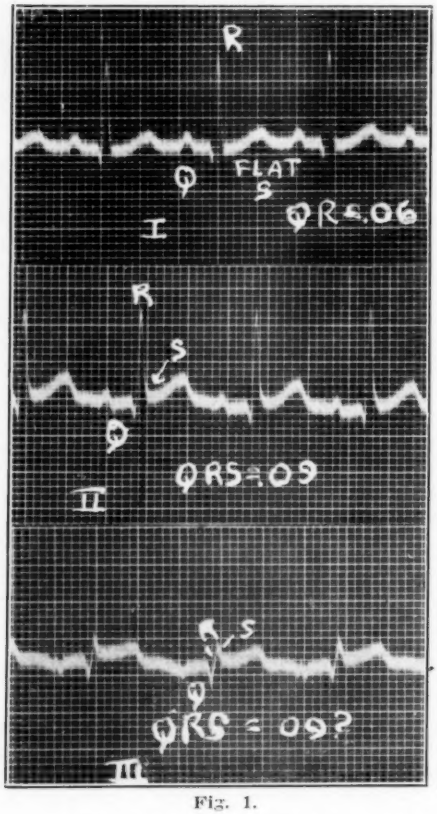

Fig. 1.

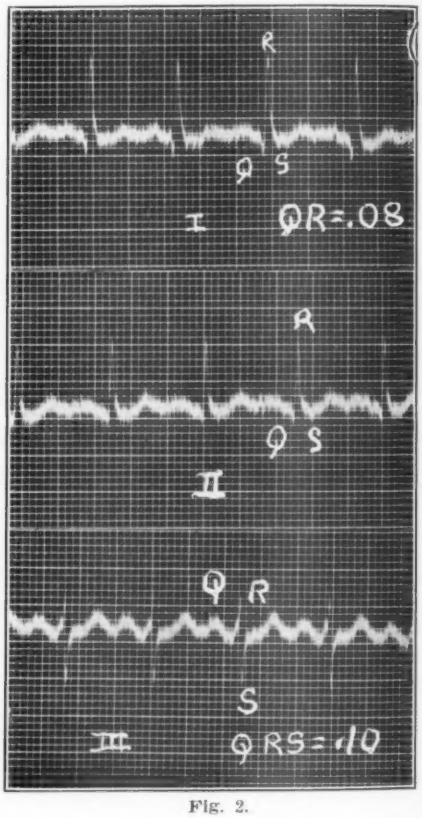

Fig. 2.

Fig. 1.—Illustrating inversion of the Q-wave in Lead I, Lead II, and Lead III. The R-wave here is considered diphasic and the S upright in Lead III.

Fig. 2.—Illustrating inverted Q-wave in Lead I, a high upward S-wave in Lead I, a slightly downward Q in Lead II, and an upright Q and R in Lead III. The S-wave in Lead III is downward. Note depth of downward S_3, which approximates upward slurring of S_1.

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horizon, there now appears to be sufficient reason for attempting this differentiation. The purpose of this paper is not to evaluate the significance of a so-called prominent Q-wave in Lead III but to point out that such in reality, rarely occurs. While the initial deflection in Lead III may fill all the requirements set down for its identification,[1] and while this electrocardiographic pattern may have some clinical significance, many of the published records[1, 2, 3, 4, 5, 6] with the so-called

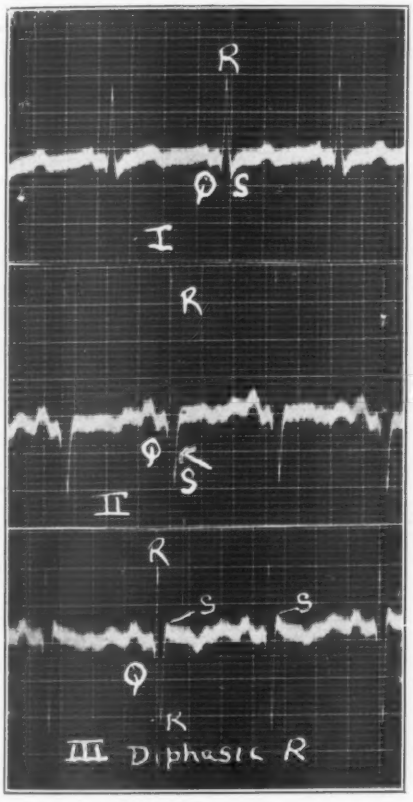

Fig. 3.

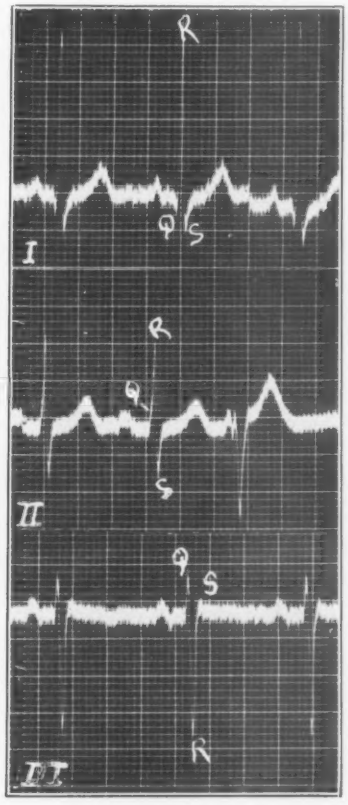

Fig. 4.

Fig. 3.—Showing down Q and S in Lead I and upright R. Further showing down Q in Lead II and diphasic R with slurred down S_2. In Lead III there is also a down Q-wave and diphasic R-wave. The S-wave is up in Lead III. This is from a case of mitral stenosis. It is unusual that all the Q-waves are downward.

Fig. 4.—Showing a downward Q in Lead I, an upward Q in Lead II slurred with the R_2, and the upward Q in Lead III with a down R_3 and an up S_3.

prominent Q_3 will be found to be either (a) a combination of an inverted Q_3 made unduly prominent by a fusion with an inverted R_3, (b) an inverted R_3 alone with an iso-electric Q_3 or (c) what I believe may be regarded as a diphasic R_3.

It appears to be the custom to call all initial upward deflections in Lead III R-waves and all secondary down deflections S-waves. Wiggers[7]

adopted Einthoven's designation of inverted initial deflections in Lead III as R-waves, although Lewis named them S-waves. In examining many published records there seems to be no uniformity in naming the various deflections, particularly of Lead III. In order that confusion may be eliminated, particularly with reference to the "prominent Q_3," some plan for this purpose should be adopted.

In records where all three waves can easily be identified, it will be found that the duration of each wave is practically constant in each

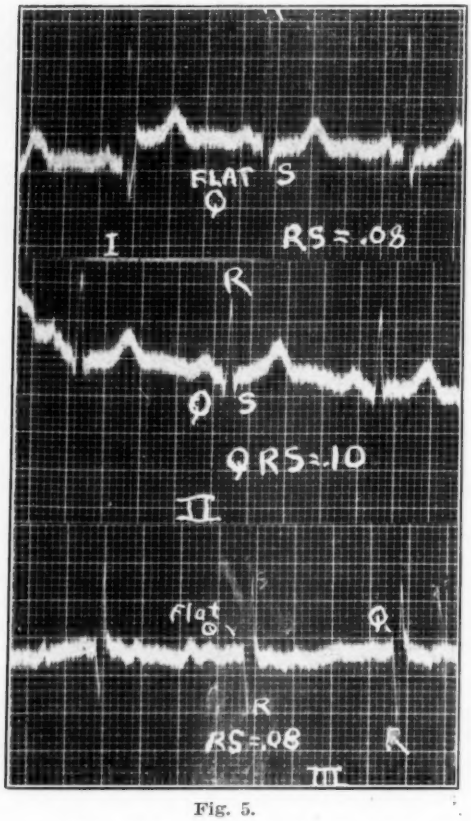

Fig. 5.

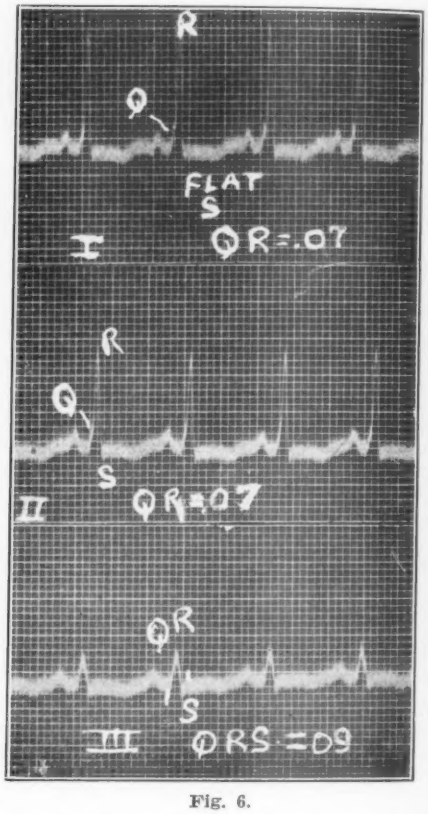

Fig. 6.

Fig. 5.—Showing no evident Q-wave in Lead I (iso-electric Q phase), a definite Q-wave in Lead II, pointing downward, and what appears to be a prominent Q_3 which is in reality a diphasic R-wave with an initial down deflection and a short up S-wave.

Fig. 6.—Illustrating an up Q-wave in Lead I, an upward Q-wave in Lead II, and apparently an upward Q-wave of Lead III. This is unusual.

lead and thus the duration of QRS is constant. The Q-wave in Lead I is apparently identified only when it points downward: the same usually holds true for the Q-wave in Leads II and III, although upward Q-waves in Lead III are occasionally designated.

In left axis deviation the Q-wave in Lead I is almost always well marked and points down. In these cases, a distinct upright initial de-

flection will be found in most instances in Lead III. In contrast to this up Q_3 in left axis deviation the Q-wave in Lead III of right axis deviation will be downward. If Lead I is examined in right axis deviation, a distinct initial upward deflection may be found in case the R-wave is inverted. If the R-wave in Lead I is slightly upright in right axis deviation, a slurring at the origin of R will be found. It is reasonable to assume this to be the fusion of an upright Q and R.

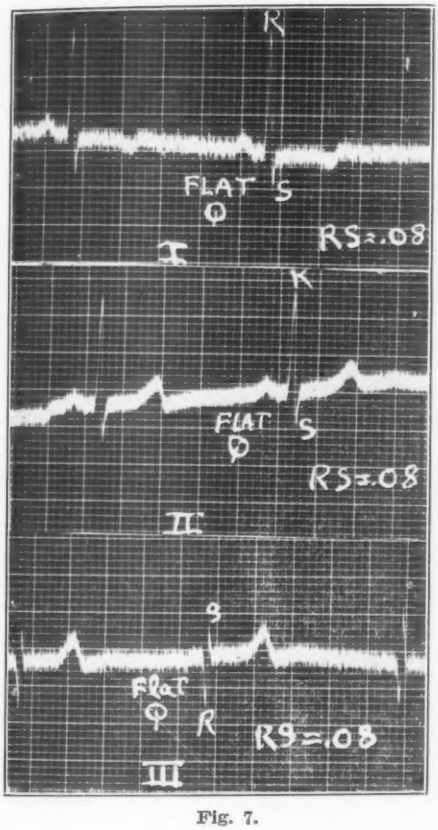

Fig. 7.

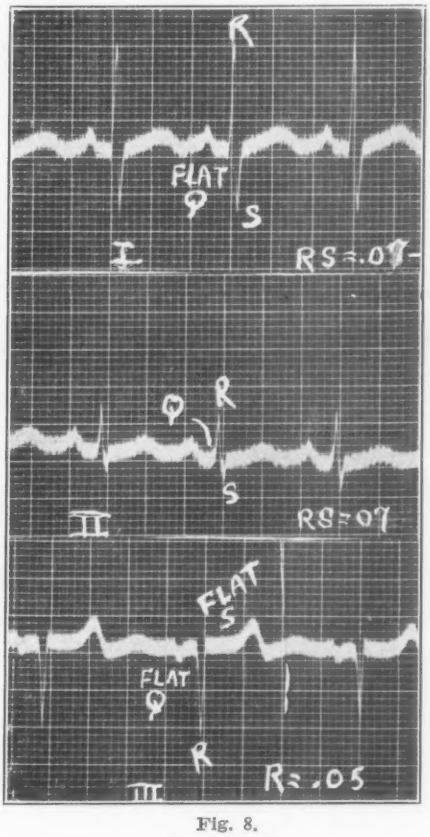

Fig. 8.

Fig. 7.—Illustrating a flat Q-wave in Leads I, II, and III (iso-electric Q phrase). The apparent Q-wave in Lead III is an inverted R-wave. The S_3 wave here is upright.

Fig. 8.—This shows a flat Q-wave in Lead I, a slightly up or flat Q-wave in Lead II and a flat Q-wave in Lead III. The apparent initial downward deflection simulating an inverted prominent Q_3-wave is an R-wave and the S_3-wave is flat. The R phrase of Lead I is diphasic. The down deflection marked "S" in Lead I is too deep for an S and if it were an S, there should be an up S phase in Lead III. Compare this record with Fig. 7, from the same patient at a later date (coronary thrombosis) in which a down S_1 and an up S_3 are easily recognizable.

If the QRS group is divided into time sections rather than deflections, and the first phase of the QRS span be considered due to Q whether it be up, iso-electric, or down, and if the R and S sections are regarded in the same manner, there should be no difficulty in many

and in fact, in most instances of being able to recognize clearly the separate components of the QRS complex.

If the so-called prominent Q-waves of Lead III are subjected to analysis in this way, it will be found that all such "Q" waves have a greater duration than is usual for a normal Q-wave, and that the actual time is often one-half or more of the total QRS duration.

Einthoven's law, Lead I + Lead III = Lead II, is applicable to the individual components of the QRS group, and it would appear that such

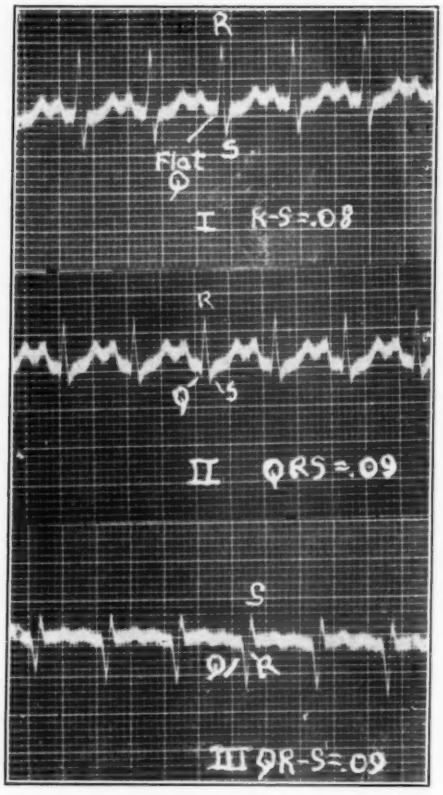

Fig. 9.

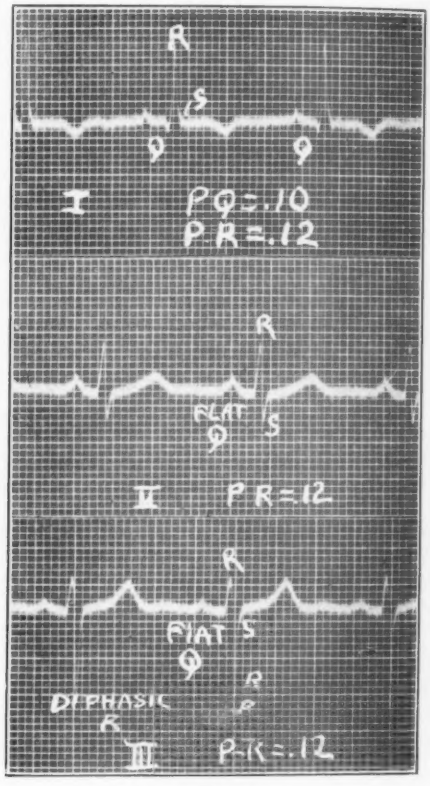

Fig. 10.

Fig. 9.—Showing a flat Q-wave in Lead I, a definitely down Q in Lead II, and a Q-wave in Lead III. The R-wave is diphasic and the initial down deflection of the R-wave is fused with the down Q-wave.

Fig. 10.—Showing a down Q in Lead I and an up S in Lead I fused with R-wave of Lead I. The R-wave in Lead III is diphasic, the S-wave in Lead III, inverted. The Q is upward in Lead III and fused with the R-wave.

application is often helpful for the correct identification of the Q-waves. In routine clinical electrocardiographic records, this law can be applied to the separate phases of the QRS group. The inability to determine this is usually due to the effect of somatic tremor or other irregularities or abnormalities which make it difficult to separate the various components.

The duration of the Q-phase can be considered usually as about one-half the duration of either R or S, so that in the total QRS phase of 0.10, the Q phase may be estimated as 0.02 seconds. By finding the greatest QRS duration of the leads and measuring backward or forward from the beginning of the Q or the end of the S in other leads,

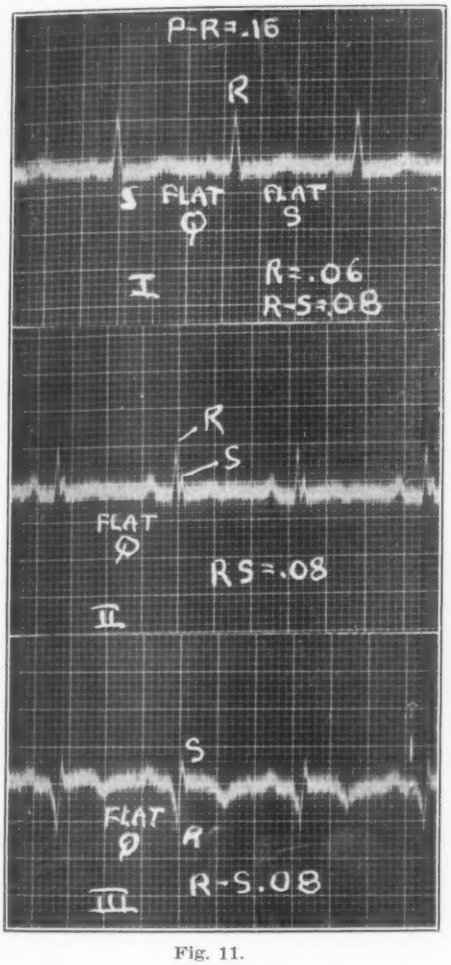

Fig. 11.

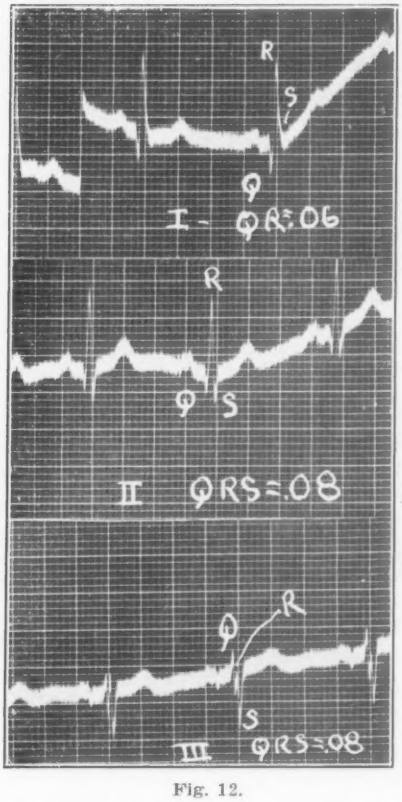

Fig. 12.

Fig. 11.—Showing again absent Q-waves in all leads and an upright R-wave in Lead I, with a flat or slightly down S-wave in Lead I. Two upright waves in Lead II, which measure to be the R- and S-waves, and then the inverted R of Lead III with the upright S in Lead III.

Fig. 12.—Illustrating inverted Q-wave pointing downward in Lead I and upright Q in Lead III. Note also the slurring of the upright S in Lead I with the R-wave, the height of which approximates the depth of the down S-wave.

the true QRS section can be laid off, and the direction of the deflection, if any, for each section can be determined.

Measurements of value may be made at times from the peak of the P-wave, if the heart rate is the same in all leads. Of course, simul-

taneous records of Leads I and III would be the best way to identify the initial waves, although it is not often necessary. For example, if a well-marked downward Q is found in Lead I, there is little likelihood of the Q pointing downward in Lead III. In such an instance, the first downward deflection in Lead III may be considered an inverted wave of the R phase, and the Q section would then be iso-electric.

In the majority of instances, the Q, R, or S phase will be either positive, negative, or iso-electric. There are times when the R-wave will

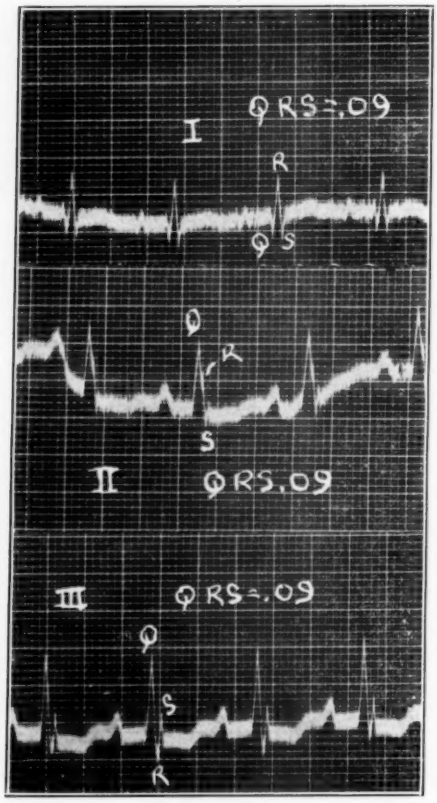

Fig. 13.

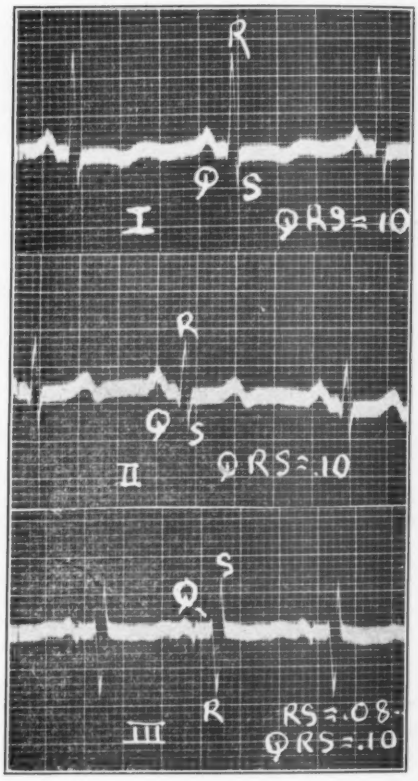

Fig. 14.

Fig. 13.—Showing a down Q_1, and up R_1, and a down S_1. In Lead II the Q-wave is up and fused with the R-wave. In Lead III the Q is also fused with the R, and the R is partially diphasic, and the S-wave in Lead III is upright.

Fig. 14.—Showing what might be interpreted as a prominent Q_3. The slightly up initial deflection in Lead III is the Q phase, and approximates the down Q excursion in Lead I. The R-wave in Lead III is diphasic and accounts for the apparently large up S phase, ordinarily called an R_3-wave.

have to be considered diphasic, yet there is no reason why this should not occur. Rarely do the Q and S phases have prominent deflections, if considered from this point of view. The R phase will be found to account for most of the great excursions of the QRS complex. Thus, if there appears to be both a positive and a negative deflection in the usual

time period of the R phase, the R-wave can thus be considered diphasic. Many instances of so-called splintered QRS complexes can be analyzed in this light.

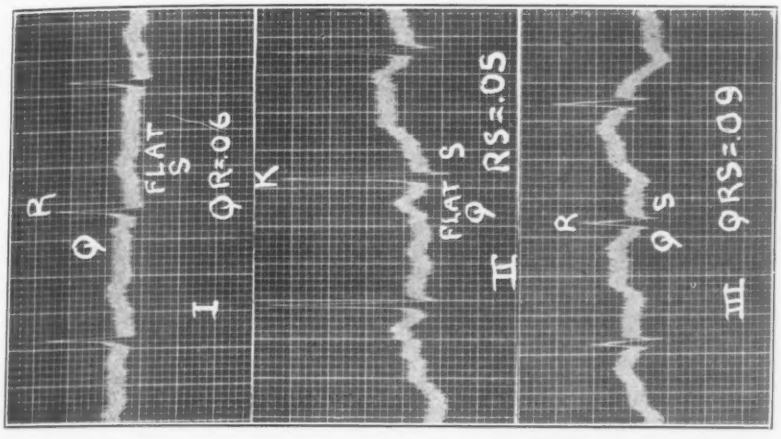

Fig. 17.

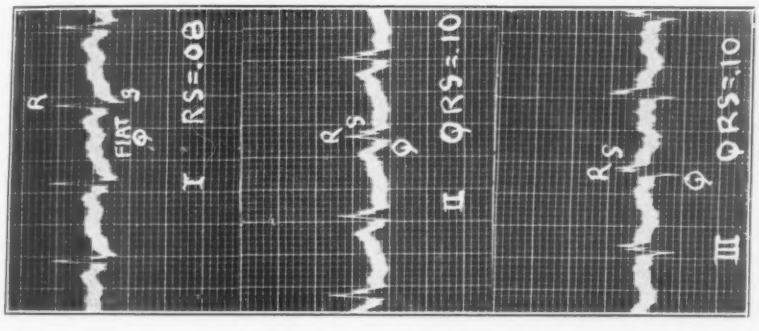

Fig. 16.

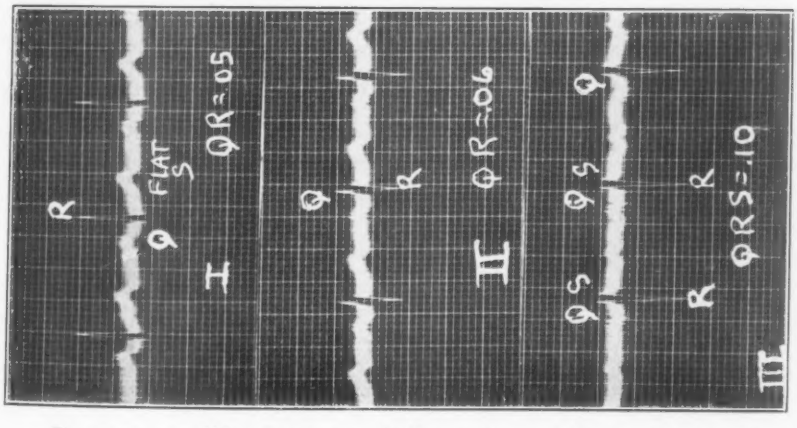

Fig. 15.

Fig. 15.—Showing opposite directions of the Q_1 and Q_3. The R-wave of Lead II is diphasic.
Fig. 16.—Showing splintered QRS of Leads II and III, also probably a true prominent Q_3-wave.
Fig. 17.—Showing an up Q phase in Lead I, causing slurring. Note absence of slurring in Lead III where the Q is opposite in direction to the R.

It seems possible that more information might be obtained in studying electrocardiograms from this viewpoint. It raises several interesting questions; for example, if the Q-wave is normally downward in

Lead I, what causes it to point upward in Lead I when right axis deviation is not present? Does the reversal of the Q direction without change

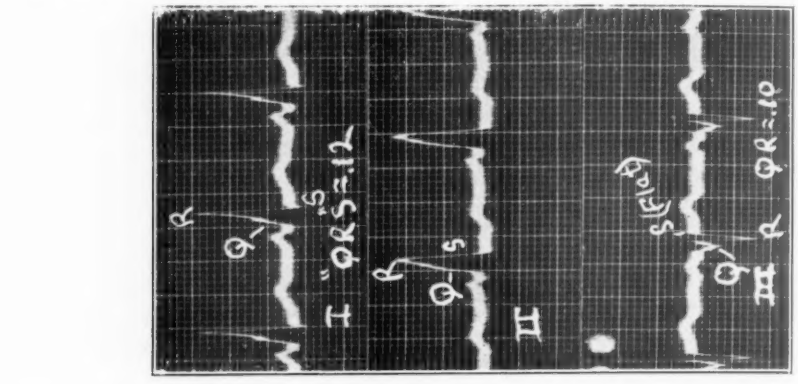

Fig. 20.

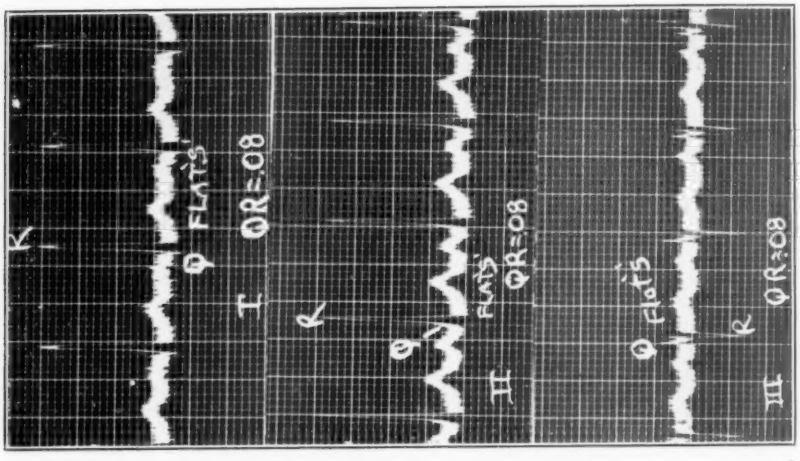

Fig. 19.

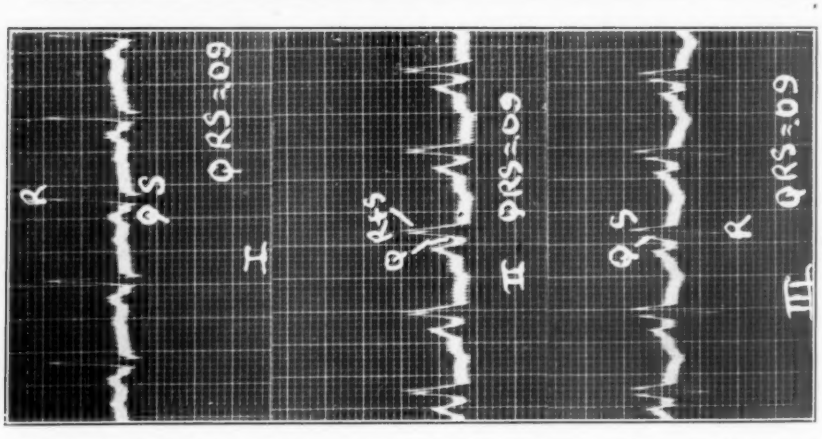

Fig. 18.

Fig. 18.—Prominent up Q_3, diphasic R_3 rendering the S_3-wave unduly prominent.
Fig. 19.—Illustrating an up Q_3-wave, a diphasic R_3-wave, and flat S phase in all leads.
Fig. 20.—Showing slurring QRS in Leads I and II, caused by wide Q section. Note the wide downward Q-wave of Lead III.

in axis deviation indicate disease in the septum? These and many other questions have come to mind in going over many tracings. Such an analysis is being undertaken. Illustrative records are appended.

CONCLUSIONS

1. The various components of the QRS are not difficult to identify in the majority of electrocardiograms.

2. It is suggested that the QRS interval be divided into three sections, and each section described as iso-electric, positive, negative, or diphasic.

3. Prominent Q_3-waves are rare. They are confused with inverted waves of the R phase of the QRS complex.

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CLINICAL DOSE AND EFFECTS OF DIGITALIS ASSAYED BY THE PIGEON METHOD*†

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PREDICTION of the clinical dose of digitalis by transfer to man of the "pigeon emetic," or minor toxicity, dose was tested previously on a group of normal subjects.[1] It was found that the intravenous emetic dose of digitalis per kilo of pigeon approximated the total clinically effective oral dose per kilo of man. This work has been continued in order to ascertain if this dosage-agreement held also for patients with cardiac disease. The matter was tested on 67 patients, and 10 normal subjects, with results believed to be worthy of record.

All the patients used had congestive heart failure; 30 of the 67 had decompensation associated with auricular fibrillation. During the investigation the patients were confined at absolute rest to their beds in the hospital. Fluid intake and urine output were measured daily. Accurately weighed quantities of powdered digitalis were administered in capsules. Two leaves of similar potency (Upsher-Smith) were tried.

TABLE I

CLINICAL RESULTS WITH DIGITALIS ASSAYED BY THE PIGEON METHOD

	LEAF I	LEAF II
Pigeon Emetic Dose (predicted total clinical dose) (mg./kg.) – E	14.0	15.0
Clinically Effective Dose, 67 patients (mg./kg.) – C	17.7	16.6
Ratio C/E	1.2	1.1
Slowing of Pulse (beats per minute)	28	24
Diuretic Action (per cent of 27 edematous patients)	77	50
Nausea or Emesis (per cent of 67 patients)	42	18
Symptoms of Digitalis Poisoning (per cent of 67 patients)	14	12
Abnormal Cardiac Rhythm Due to Poisoning (per cent of 67 patients)	8	6

An intensive method of medication was followed throughout as in the previous study; i.e., one-half the estimated total dose was administered at once, one-fourth at the end of four hours, and thereafter one-eighth every three hours until definite signs of digitalis action occurred. Accordingly, errors in clinical dosage plus or minus 12 per cent would be expected, but this was regarded as satisfactory enough under the conditions. The criteria of digitalis action were: slowing of the pulse;

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decrease in venous pressure, as indicated by decreased vein-distention and by venous pressure determinations; relief from dyspnea, general improvement of the patient; increased diuresis in edematous patients; minor toxic actions, such as loss of appetite, nausea, and vomiting; and cardiac arrhythmias. A summary of the essential data and comparisons is presented in Table I; the results in all cases represent averages.

COMPARATIVE DOSES

Leaf I, assayed by the pigeon method, had a M.Em.D. (minimum emetic dose) of 14 mg. per kilo. The average dose required for clinical improvement in 30 patients was 17.7 mg. per kilo, or 26 per cent more than the dose estimated by the pigeon method. The range of clinically effective doses was wide; between 29.6 and 10.2 mg. per kilo, a difference exceeding 190 per cent. Wide variation in clinical dosage of digitalis is a matter of common knowledge, and is due to a number of uncontrollable factors, such as individual susceptibility, irregularities of gastrointestinal absorption, etc.

Leaf II had a M. Em. D. of 15 mg. per kilo. The clinically effective dose, assayed on 27 patients, was 16.6 mg. per kilo, or 11 per cent more than the pigeon emetic dose. The range of clinical doses again proved large; i.e., from 6 to 28.6 mg. per kilo, a difference of over 370 per cent.

In the standardization of digitalis with pigeons it was observed by Hanzlik[2] that the minimum emetic dose was somewhat higher for males than for females. No such difference in sexes was observed in human subjects, the average dose of digitalis for 35 males being 17.6 mg., and for 32 females 17.9 mg., per kilo.

Ten other subjects with apparently normal cardiovascular systems were given Leaf I. The average dose which caused slowing of the pulse, anorexia, and slight nausea was 24 per cent higher than in patients with congestive heart failure. The normal subjects required 22 mg. per kilo as compared with 17.7 mg. per kilo for those with pathological conditions.

According to these results, the clinical doses of the two samples of digitalis leaves had a fairly constant ratio to the pigeon emetic dose, namely, 1.2 and 1.1; unity would indicate perfect agreement. Accordingly, the pigeon dose gives all that could be expected of a bio-assay method on animals. While any bio-assay method is useful for comparing the potency of one digitalis product with another, the choice would naturally fall on the easiest and most economical method, and such is the pigeon method. Burn[3] has shown that the pigeon method is as satisfactory as the cat method for bio-assay purposes. Confirmations of the value of the pigeon method have also been made by Guidi[4] and by Carratala.[5] From the clinical data obtained, it is apparent that the pigeon-emetic dose in milligrams per kilo may be transferred directly to

milligrams per kilo body weight of patient, since the pigeon-clinical dose ratio approaches unity. The margin of therapeutic safety would be indicated by the ratio of pigeon-emetic and fatal doses.

Comparisons of the clinically effective doses with cat-fatal doses[6] have not been made by me, since the assays with cats in this laboratory have been too variable,[7] and the median doses have exceeded those frequently reported by others.[8] For instance, the cat-fatal dose of Leaf I was a median of 108 mg. per kilo (range 87 to 190 mg.; 8 cats), while the fatal dose given on the container was 88.5 mg. per kilo. The ratio of the predicted clinical dose from the former cat dose to that found would be 0.55, and from the latter cat dose, 0.67, which is poor as to agreement of values and as to comparability with the pigeon-clinical ratio. Assays on significant numbers of cats, comparable with the dozens of pigeons used in our assays, are not practically feasible, and therefore, the pigeon doses are more accurate. The practice of selecting doses is scientifically unjustifiable with any bio-assay method.

CLINICAL EFFECTS

The great range of effective dosage in man has been observed before. Obviously, there is no method of bio-assay which can determine the dose for the individual patient when variations of nearly 200 to over 300 per cent occur with the same leaf in different human subjects. In spite of the most accurate assay, each patient must be observed closely for signs of digitalis action. The dose must be determined solely by the clinical response of the individual patient, regardless of the potency of the digitalis. The value of bio-assay lies in the reduction of error in dosage from several thousand per cent (between various digitalis preparations) to two or three hundred per cent (due to variations in individual susceptibility). The pigeon-emetic dose, which is a minor toxicity dose, should come close to indicating the probable limit of the total clinical therapeutic dose, as indeed it appears to do, according to the typical signs and symptoms of digitalis action observed in this study. Known conditions, such as altitude, which increases the emetic and toxic actions of digitalis, should be taken into account when estimating the clinical dose.[7]

Slowing of the pulse is one of the most valuable practical signs of digitalis action. This slowing occurs also in normal persons, although the dosage required to produce the change is somewhat higher than in those with a pathological condition.[1, 10]

Nausea, and especially vomiting, are to be avoided if possible. Sixty per cent of all my patients (Leaf I, 48 per cent and Leaf II, 12 per cent) experienced loss of appetite or nausea, while 28 per cent vomited one or more times. Starnotti,[9] who tried pigeon-emetic doses of a number of digitalis specialties in 15 patients, observed similar symptoms in

40 per cent of his patients. He stated that his clinical experiments demonstrated the reliability of the pigeon method of digitalis assay, but he doubted the advisability of the intensive administration as a standard system of dosage.

Of the 67 patients, only 8 experienced more or less intense digitalis poisoning; 4 of these showed cardiac irregularities, consisting of extrasystoles, heart-block, and 1 showed bigeminal rhythm. Three of these patients were later found to have had digitalis before entering the hospital, but poisoning in the other 5 patients was due to failure to adhere to the proper technic of medication, and could have been avoided.

Diuretic action occurred in 64 per cent (average of 77 and 50 per cent) of all patients having congestive heart failure and edema. No increase in urine output occurred in normal subjects receiving digitalis. Digitalis-diuresis has been discussed in a previous paper.[10]

CONCLUSIONS

1. The ratios of clinically effective doses of 2 digitalis leaves, in 67 patients, to the pigeon-emetic doses were found to be 1.2 and 1.1. The actual clinically effective doses were 17.7 and 16.6 mg. digitalis per kilo body weight, a remarkably good agreement with the pigeon doses.

2. About 60 per cent of all the patients showed minor symptoms of toxicity, such as nausea, and 28 per cent vomited, after oral doses of digitalis equal to the intravenous pigeon-emetic dose per kilo body weight. Only 8 of the 67 patients showed evidences of digitalis poisoning with this dosage. These side-actions testify that the pigeon-emetic dose results in definite systemic absorption and action of digitalis.

3. The pigeon method fulfills all that can be reasonably expected of a bio-assay method on animals, which would predict the probable full therapeutic dose, and it is the easiest and most economical of all bio-assay methods.

4. The wide range of dosage required to secure full therapeutic effects of digitalis in man emphasizes the importance of close clinical observation during medication, even though a standardized preparation is used.

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THE EFFECT OF ADENOSINE ON CARDIAC IRREGULARITIES IN MAN*

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IT HAS been recently observed by Drury and Szent-Gyorgyi that adenosine may restore sinus rhythm in the heart of animals in which auricular fibrillation has been produced experimentally. As the use of such a drug which could restore the normal mechanism of the heart in man would be of great value, we undertook the investigation of the action of the drug in several patients with abnormal rhythms of the heart.

Adenosine is a yeast nucleic acid derivative, and its chemical and its biological properties have already been described by Drury and Szent-Gyorgyi.[1] The effect of adenosine and its related compounds may be summarized as follows.

These drugs slow the rate of beating in normal sinus rhythm. They impair conduction from auricle to ventricle, arrest experimentally induced auricular fibrillation, shorten the refractory period in high rates of beating, and improve slowed rates of intra-auricular conduction. They also dilate the coronary, renal and splanchnic arteries and cause a drop in arterial blood pressure. The effect is transient and is completely over in from forty to sixty seconds. In the guinea pig this group of drugs produces a partial heart-block. Atropine does not abolish the disturbances in heart rhythm induced by these drugs. Barium salts do, however, inhibit the action of these related drugs in the animal.

Honey and his coworkers[4] were not successful in arresting auricular fibrillation in man after the administration of 50 mg. of adenosine. They do not report, however, whether the auricular fibrillation in their cases was paroxysmal or permanent. It is important to appreciate this, since only the transient type of auricular fibrillation responds to adenosine, as shown by the experimental work of Drury and Szent-Gyorgyi.

METHOD OF STUDY

Adenosine was administered to seven patients with heart disease and to one patient with pulmonary tuberculosis, all of whom developed ectopic rhythms while under observation at the Montefiore Hos-

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pital. In none of the cases were the ectopic rhythms the result of drug therapy. Four of the patients, one with auricular fibrillation, two with auricular tachycardia, and one with a supraventricular type of tachycardia, had been observed during previous paroxysmal seizures of these arrhythmias. Pressure over the carotid artery restored normal sinus rhythm in only one of the eight cases with arrhythmias.

The doses of adenosine varied from 5 to 50 mg. Doses of less than 15 mg. were not effective even when given intravenously. The subcutaneous and intramuscular administration of the drug up to 50 mg. was also ineffective. All of the observations which are being reported followed the intravenous administration of the drug.

Control electrocardiograms were obtained before, during, and after the administration of the drug for periods varying from one to three hours.

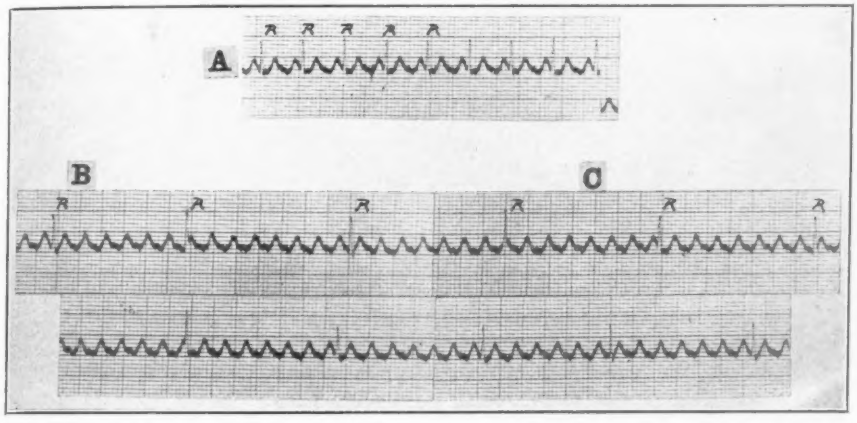

Fig. 1.—The effect of adenosine on flutter of the auricles. *A*, Control before adenosine; *B* and *C*, after adenosine.

The following is a report of some of the correlated observations we made during this investigation.

OBSERVATIONS

I. *The Effect of Adenosine on Auricular Flutter.*—A female, twenty-five years of age, with chronic rheumatic heart disease and mild congestive heart failure, developed a paroxysm of flutter of the auricles with the ventricles beating at the rate of 210-230 per minute and the auricles beating at the rate of 420 per minute.

Shortly after the onset of the paroxysm 35 mg. of adenosine were given to her into the antecubital vein. Ten seconds after the injection the ventricular rate suddenly dropped from 210 (Fig. 1 *A*) to 80 beats per minute and continued to beat between 80 and 100 beats per minute for the next forty seconds (Fig. 1 *B*, *C*). Then the ventricular rate gradually increased until it reached its pre-injection level of 210 beats per minute, twenty seconds later.

The electrocardiogram shows a marked increase in block, appearing ten seconds after the injection (Fig. 1 *B*) and lasting sixty seconds. The rate of the flutter

of the auricles is not altered (Fig. 1 *B, C*). The greatest increase in block occurs fifteen to thirty-five seconds after the injection, when the ventricles responded to every seventh or eighth impulse which arises in the auricles (Fig. 1 *C*). The block then diminishes until the 2:1 block is re-established at the end of sixty seconds. The ventricular complexes are not altered in shape, size, or form.

Comment.—The effect of adenosine in auricular flutter is predominantly on the junctional tissue, as is shown in the accompanying electrocardiograms. There is no effect on the rhythm of the auricles in this case. This is in agreement with the conclusions drawn from the experimental work in animals where the influence of adenosine is principally on the sino-auricular and auriculoventricular nodes.

II. *The Effect of Adenosine on Paroxysmal Auricular Fibrillation.*—A male, aged fifty years, with chronic coronary vessel closure developed frequent seizures of paroxysmal auricular fibrillation. Large doses of digitalis did not diminish the frequency or the duration of the attacks. Pressure over the carotid arteries had no effect on the rhythm.

Soon after the onset of one of the paroxysms of irregular rhythm we administered intravenously 20 mg. and 30 mg. respectively of adenosine. The 30 mg. dose was given one-half hour after the administration of the smaller dose which did not produce any clinical or electrocardiographic changes. The administration of larger dose of the drug was followed by a short period of bradycardia, but the rhythm of the auricles was not altered.

Soon after the onset of another of the paroxysms of the irregular rhythms, we administered intravenously 45 mg. of this drug. Ten seconds after the administration of this dose the patient complained of precordial pain, giddiness, and faintness. The heart rate suddenly dropped from 100 beats per minute to 40 beats per minute, and at fifteen seconds after the injection the heart sounds became inaudible and the pulse imperceptible for a period of four seconds. Then the heart sounds were again heard beating at a slow rate and gradually increasing in speed until at the end of forty-five seconds the heart rate was again at its pre-injection level. The precordial pain, giddiness, and faintness disappeared when the heart rate had increased to 60 beats per minute. The rhythm remained irregular.

The electrocardiograms show a lengthening of the R-R period from 0.5-0.7 seconds to 0.7, 0.9 and 1.6 seconds in successive beats followed by a period of asystole of the ventricles of 4.6 seconds' duration. A normal supraventricular complex ends the asystolic period and is followed by an ectopic beat, arising in the ventricles. The ventricular beats now appear more regularly at intervals of from 1.4 to 1.9 seconds until 52 seconds after the injection when the R-R intervals gradually decrease to the pre-injection ventricular rate. The fibrillation of the auricles is not affected.

Comment.—In a patient suffering from paroxysmal auricular fibrillation the auriculoventricular block was markedly increased for a period of 60 seconds after the administration of the drug. At 20 seconds the ventricles did not respond for a period of 4.6 seconds, and then the ventricles beat at the rate of only 30 to 40 per minute. The auricles continued to fibrillate.

III. *The Effect of Adenosine on Sinus Rhythm.*—In the same patient, thirty-five mg. of adenosine were given during the phase of normal sinus rhythm. The patient complained of marked giddiness, precordial pain, and faintness beginning about ten seconds after the injection. This lasted for 20 seconds. During this period the pulse was imperceptible (Fig. 2 *B*) and the heart sounds were not heard. The first ventricular contraction after the pause was followed quickly by a second pause.

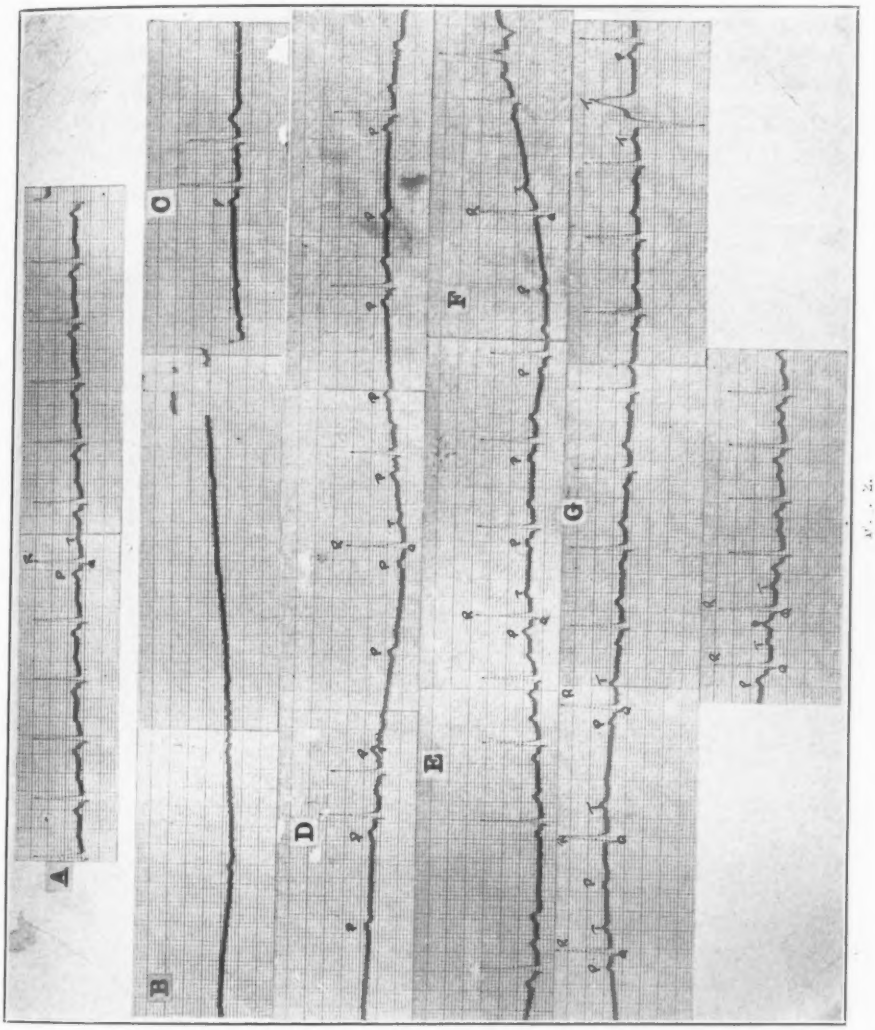

Fig. 2.—The effect of adenosine on paroxysmal sinus rhythm. *A*. Before adenosine; *B*, ten seconds after 35 mg. of adenosine; *C*, fifteen seconds after adenosine; *D*, twenty-three seconds after adenosine; *E*, forty seconds after adenosine; *F*, forty-five seconds after adenosine; *G*, fifty-five seconds after adenosine.

Then there was another pause for 3 seconds. During this period the patient complained of the same symptoms as described above (Fig. 2 *C*). The pulse continued beating at the rate of 25-50 beats per minute for 25 seconds; then it increased in rate to the pre-injection level (Fig. 2 *C*, *D*, *E*).

The electrocardiograms show a period of ventricular asystole of 9.2 seconds (Fig. 2 *B*) followed by periods of 2-3 seconds of ventricular asystole (Fig. 2 *C*). The auricles continued beating at the rate of 90 per minute and each second to third beat was followed by a ventricular complex (Fig. 2 *D*). The P-R interval remained constant at 0.17-0.2 seconds. The normal auriculoventricular conduction was restored for a short period (Fig. 2 *E*), following which the auricular rate was slowed from 90 beats per minute to 70 beats per minute and the conduction from auricle to ventricle was again prolonged. This was accompanied by a dissociation between auricles and ventricles for a period of 5 seconds (Fig. 2 *F*) after which normal sinus rhythm was again restored (Fig. 2 *G*).

Comment.—The development of partial heart-block for a short period of time after the apparent recovery of normal conduction reproduces in man the same delayed effect of the drug, as is shown by Drury and Szent-Gyorgyi to be present in the animal.

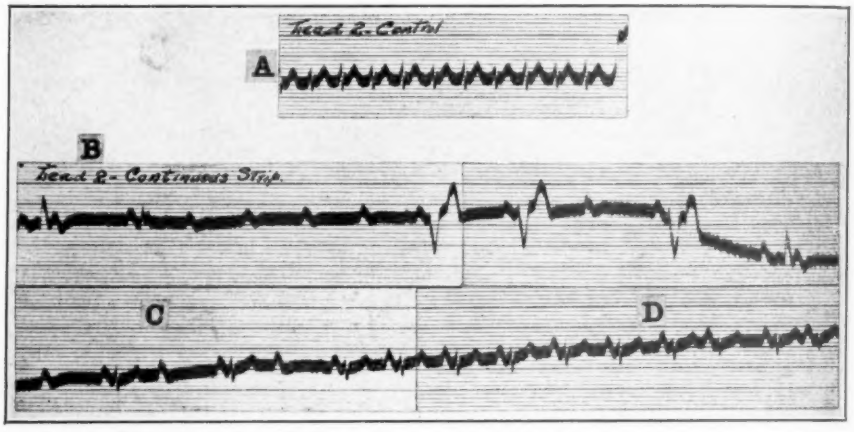

Fig. 3.—The effect of adenosine on paroxysmal tachycardia of auricular origin. Case 1. *A*, Control record, before adenosine; *B*, twelve seconds after adenosine; *C*, twenty seconds after adenosine; *D*, twenty-five seconds after adenosine.

IV. *The Effect of Adenosine on Paroxysmal Tachycardia of Auricular Origin.*—CASE 1.—A male, aged fifty years, who had moderately advanced pulmonary tuberculosis, also suffered from frequently recurring episodes of paroxysmal tachycardia. The paroxysms ended spontaneously one to three days after their onset. Digitalis and quinidine had no effect on the frequency and duration of recurrences of the ectopic rhythm.

Thirty mg. of adenosine were administered intravenously soon after the onset of a recurrence of the ectopic rhythm when the heart action was regular and the rate of beating was 210 per minute (Fig. 3 *A*). Ten seconds after the administration of the drug, the patient complained of giddiness and faintness which lasted for a few seconds. The pulse slowed after 10 seconds (Fig. 3 *B*), then became imperceptible for about 3 seconds, reappeared beating at a slow rate and then the rate gradually increased until it reached the pre-injection rate of 210 beats per minute.

The electrocardiogram shows a slowing of the auricular rate, coming on ten seconds after the injection, followed by complete dissociation between auricles and ventricles for 8 seconds (Fig. 3 *B*). At the same time as the auricular rate increased,

the complete auriculoventricular block changed to partial (2:1) auriculoventricular block (Fig. 3 *C*). After 25 seconds normal conduction was restored, the heart beating at 150 per minute (Fig. 3 *D*).

Comment.—In a patient with auricular tachycardia the heart rate was temporarily reduced from 210 to 150 beats per minute after the administration of 35 mg. of adenosine. The coincidental increase in the auricular rate and decrease in the auriculoventricular block is due to the decrease in the effect of the drug as its effect is dissipated on the heart.

CASE 2.—Male, aged forty years, with hypertension, had several seizures of paroxysmal tachycardia which disappeared on one occasion following the application of pressure over the right carotid artery and on the other occasions ended spontaneously. Digitalis had not ended the ectopic rhythm on one trial when a larger dose of the drug was given.

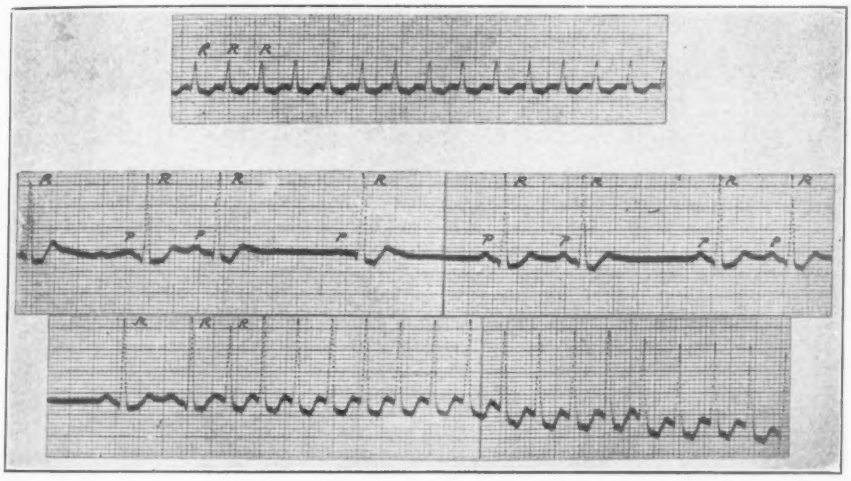

Fig. 4.—The effect of adenosine on paroxysmal tachycardia of auricular origin. Case 2.

Thirty-five mg. of adenosine were administered intravenously soon after the onset of a paroxysm of tachycardia. Although there were pulse pauses of 2-3 seconds' duration, the patient did not complain of any of the subjective effects of the drug.

The electrocardiogram shows a marked depression of the sinus node with periods of standstill of both the auricles and ventricles of one to two seconds. There is no dissociation between auricles and ventricles. The pre-injection heart rate is restored after about 40 seconds (Fig. 4).

V. *The Effect of Adenosine on Tachycardia of Supraventricular Origin.*—In a female, aged fifteen years, with rheumatic carditis, 25 mg. of adenosine were given shortly after the onset of nodal tachycardia. There were no clinical or electrocardiographic changes noted to follow the administration of the drug.

Comment.—Drury and Szent-Gyorgyi have shown experimentally that adenosine has no direct action on the ventricles in animals. It is therefore not surprising that the drug did not have any action in this case.

SUMMARY AND CONCLUSIONS

1. Adenosine was administered intravenously in doses varying from 25 to 45 mg. in eight patients who developed paroxysmal tachycardia while under observation at the hospital.

2. In paroxysmal auricular flutter and in paroxysmal auricular fibrillation, the drug increased the grade of auriculoventricular block for from 40 to 60 seconds. The abnormal rhythm was not abolished.

3. In paroxysmal tachycardia of auricular origin the drug temporarily abolished the ectopic rhythm in one case, and was ineffective in restoring sinus rhythm in a second case.

4. In paroxysmal tachycardia of supraventricular origin there was no effect on the rate or rhythm of the heart.

5. Ventricular standstill for periods of 1-9.2 seconds followed the administration of the drug in the cases with abnormal rhythms of auricular origin. During these periods the patients experienced giddiness, faintness, and precordial pain. The symptoms disappeared with the return of ventricular contractions.

6. In man, adenosine is of doubtful therapeutic value in paroxysmal tachycardia of auricular origin and of no therapeutic value in the other ectopic rhythms which we have studied.

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ELECTROCARDIOGRAPHIC STUDY DURING A PAROXYSM OF ANGINA PECTORIS*

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FROM animal experimental work, as yet unpublished, we have concluded that electrocardiographic changes characteristic of those encountered in angina pectoris can be produced by anoxemia. We have by general anoxemia and by transient coronary constriction altered the terminal deflections and affected the normal paths of intracardiac conduction. When adequate oxygenation was restored, the curves returned to normal. Our results agree with those of Kountz and Gruber.[1]

Recently we have had the opportunity to take tracings of a patient during an anginal attack. The alterations in the terminal deflections were identical with those we produced experimentally in animals and they were transitory. Within two minutes after the anginal seizure the record was essentially normal. It is our feeling that these alterations were due to anoxemia.[2]

CASE REPORT

The patient walked into the electrocardiographic laboratory on January 6, 1933, to have the routine tracing made. The three standard leads were taken (Fig. 1). The rhythm was regular, the rate was 90, and the A-V conduction time was normal. In Lead II the T-waves were flattened; they were negative in Lead III. Lead III also showed deepened Q-waves. Slurring of the QRS complexes occurred in all leads.

While the electrodes were still attached he spontaneously developed a paroxysm of substernal pain, typical in all respects of those he had been suffering. A tracing taken at this time (Fig. 2) showed: regular rhythm, rate 75, and normal A-V conduction time. The S-T intervals in Leads II and III had become elevated and in Lead I had become depressed.

Two minutes later, when the attack had spontaneously subsided, a third tracing (Fig. 3) showed: regular rhythm, rate 83, and normal A-V conduction time. The Q-wave in Lead II was deepened. Lead II was the only one recorded.

Thanks to Dr. Joseph Kaufmann, who had referred this patient, we were able to obtain tracings on April 29, 1933. They showed (Fig. 4) regular rhythm, a rate of 75, and normal A-V conduction time. The T-waves were diphasic in Lead II, and negative in Lead III. The Q-waves were deepened in Leads II and III, and there was slurring of the QRS complexes in all leads.

The patient, M. F., a business man, sixty-one and one-half years of age, was referred by Dr. Kaufmann because of chest pain. Prior to 1928, he had enjoyed

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good health. At this time he began to suffer from what was thought to be cardiospasm in spite of the negative findings in x-ray films of the gastrointestinal tract.

Substernal pain first appeared on the evening of January 1, 1933. While walking in the bitter cold he was seized twice with attacks of severe cramplike pain beneath the lower sternum. With each paroxysm he had to stop and rest until it ceased. The pain did not radiate.

The next day and for succeeding days thereafter, the pain recurred on the average of four to five times a day as he went about his usual business. During this time the character of the paroxysms remained constant. It was five days after the onset of the angina that we obtained tracings.

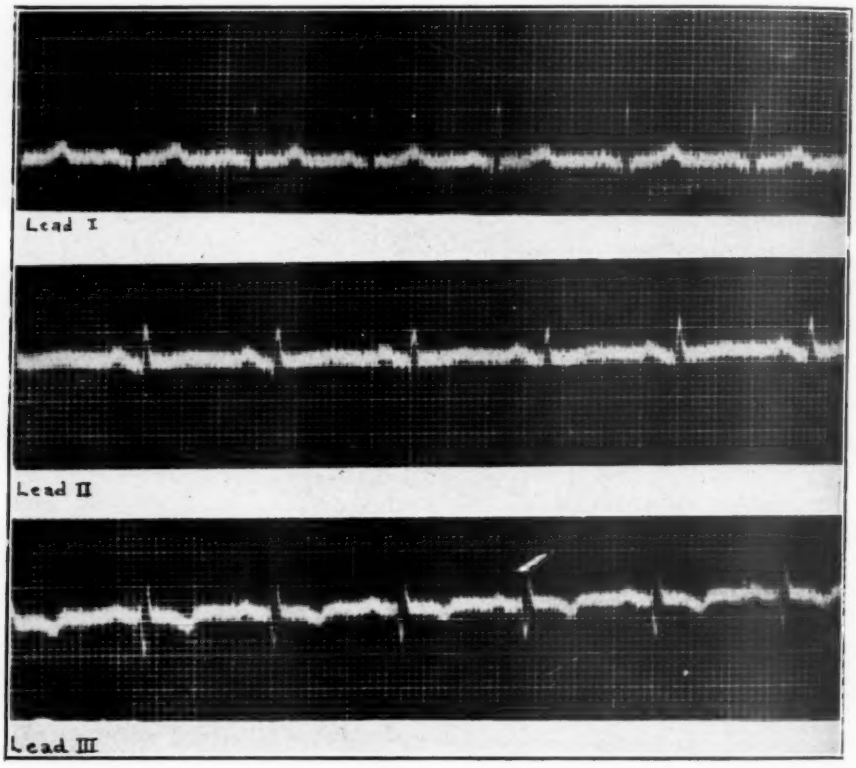

Fig. 1.—Electrocardiogram, three standard leads, taken from patient, M.F., January 6, 1933, just prior to an attack of angina pectoris. Regular rhythm, rate 90, normal A-V conduction time, flattened T-waves in Lead II, negative T-waves Lead III, deepened Q-waves Lead III, slurring of QRS complexes.

From January 6 to January 12, although he rested at home, the attacks continued, coming usually after meals or when he had gotten up to go to the bathroom. On January 13 he was free from pain, and, after four days' further rest, he returned to work. Since this time he has carried out his usual activities with but minor modifications. There have been occasional periods when he has had a sense of mild substernal constriction from overexercise, but there have been no further severe seizures of pain.

He stated that he had never had shortness of breath, headaches, cough or swelling of the ankles and feet. He slept on one pillow. He estimated that he was six pounds under his usual weight.

On April 29, the area of relative cardiac dullness extended from the third left rib downward, bounded by the right sternal border and running 13.5 cm. to the left of the midsternal line when horizontal, and 12 cm. from the same point when erect. There was no widening of the mediastinal dullness in the second interspaces.

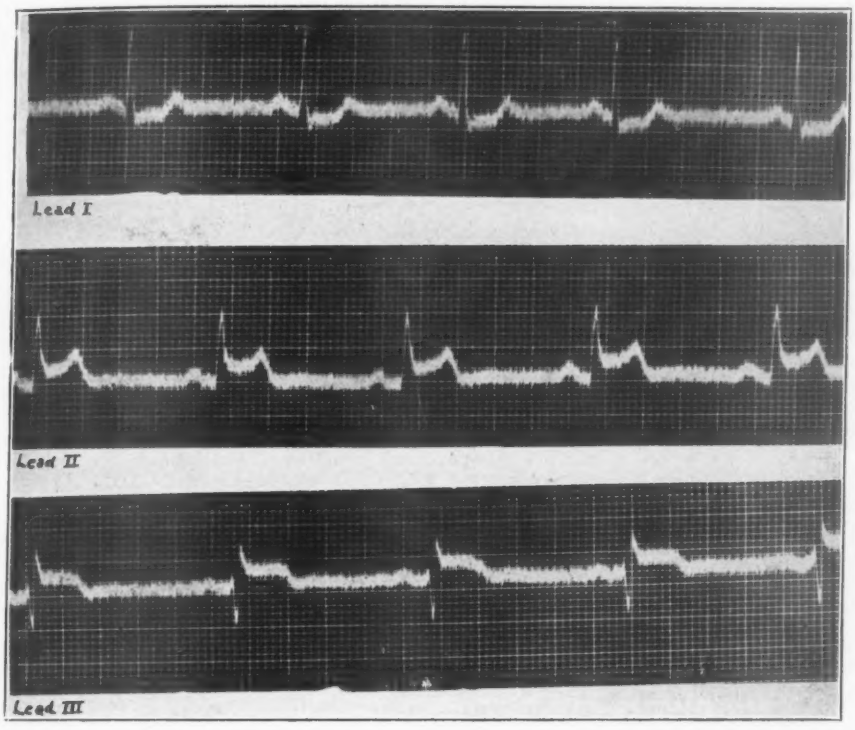

Fig. 2.—Tracings taken of the same patient on the same day, during the height of one of his characteristic seizures of substernal pain. Observe the coronary T-wave type of deviations and compare with the tracing of Fig. 1 and Fig. 3 taken a few minutes before and after the paroxysm. Regular rhythm, rate 75, normal A-V conduction time, elevation of "S-T" intervals in Leads II and III with depressed S-T in Lead I.

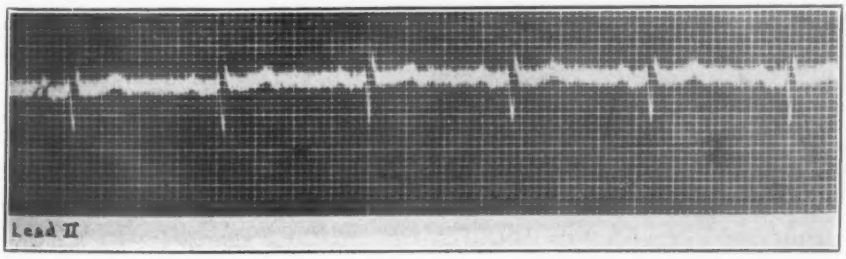

Fig. 3.—Lead II taken less than two minutes after the seizure. Regular rhythm, rate 83, normal A-V conduction—deepened Q-waves in Lead II.

The heart sounds were somewhat distant but were clearly heard. They were less audible at the apex than at the base. The aortic second sound was somewhat louder than the first sound which was associated with a faint blowing systolic murmur. The radial pulses were equal and were of good volume and tension. The heart rate was 74. The systolic blood pressure was 132 mm.; the diastolic 65. There

was no evidence of venous pressure elevation. The vessel walls were moderately thickened. There was no definite arcus senilis.

X-ray films of the heart taken at six feet showed the greatest transverse diameter was 17 cm.; the greatest oblique diameter 17.5 cm. The transverse chest diameter was 29 cm. The greatest transverse diameter of the aorta was 6.5 cm. From the x-ray plates, the enlargement of the heart was greatest to the left of the midsternal line.

There was nothing of note in the remainder of the patient's history or examination. The cranial nerves, deep and superficial reflexes showed nothing unusual. The specific gravity of the urine was 1.018. There was a trace of glucose, no albumin, and nothing abnormal microscopically. The Wassermann reaction was negative.

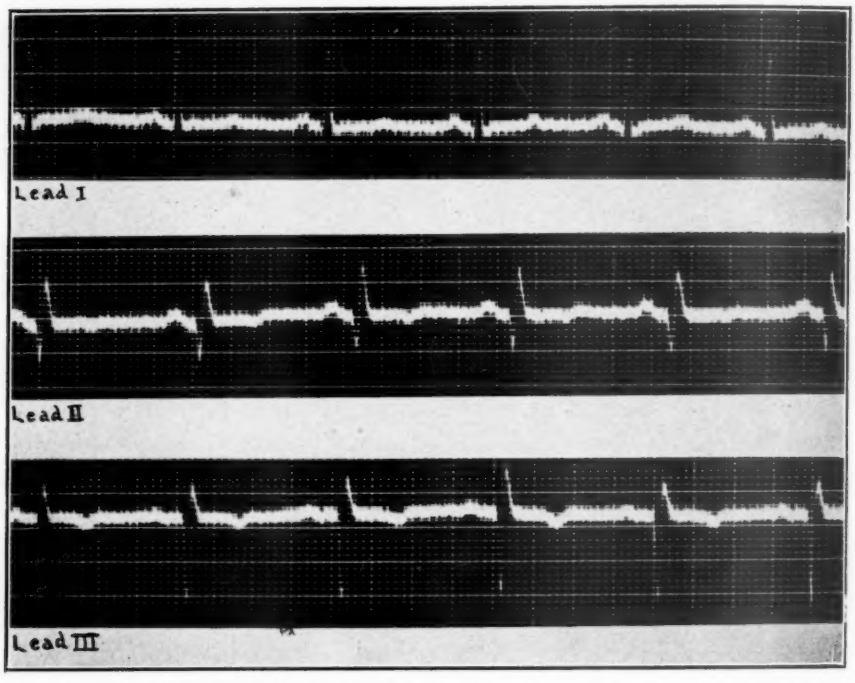

Fig. 4.—Tracings taken April 29, 1933, nearly four months later. Regular rhythm, rate 75, normal A-V conduction time, diphasic T-waves Lead II, negative T-waves Lead III, deepened Q-waves Leads II and III, slurring of QRS complexes.

COMMENT

From the clinical standpoint this patient had moderate peripheral and coronary arteriosclerosis. The heart was somewhat enlarged. The anginal attack which we observed and during which we obtained tracings could not have been due to coronary thrombosis, though the record (Fig. 2) is typical of this condition. Transitory changes of this type must be the result of alterations in the coronary circulation which have caused temporary anoxemia of the myocardium.

We interpret the differences between the curves in Fig. 1 and those of Fig. 2 as evidence of a relatively rapid advance in coronary disease. Whether there had ever been an infarction cannot be proved. The

patient suffered a minimum of fifty severe seizures, and he cannot be persuaded that any one was different from the others. The increased deepening appearing in the Q-waves of Leads II and III is a notable feature in the light of recent work.[3]

The fact that alterations occurring during the attack (Fig. 2) are not secondary to changes in the QRS complexes is important.[4]

We regret that only Lead II was taken on recovery from the seizure (Fig. 3), but, since some of the most marked changes were present in this axis, we think it should be allowed to stand as evidence of recovery. We feel that records taken a few minutes later would have shown a complete reversion to those in Fig. 1.

DISCUSSION

Electrocardiograms taken during seizures of angina pectoris, that have been described in the literature, fall into three groups: those which show primary deviations in the terminal deflections only,[5, 6, 7, 8, 9, 10] those which show the bizarre deviations of intracardiac conduction block in one of the bundle branches,[11, 12] or in the bundle itself,[13] and lastly those which showed no deviations at all. All three of these groups also appear with coronary thrombosis. In fact, we have concluded that there is only one constant differential point and that is the length of time the changes persist. In coronary thrombosis they last for days but tend to return toward normal in weeks or months; in angina pectoris the return takes only a few minutes. Our case, for example, had recovered in less than two minutes.

A second classification of published cases can be made into two groups: those which were recorded during spontaneous seizures, and those in whom seizures were artificially produced by unusual exercise. We feel that there may be good reason for studying the two groups separately. An entirely different mechanism may be operating in each to produce the attack—possibly a coronary vasospasm in the first group producing localized areas of ischemia, while in the second group a total relative myocardial ischemia is produced by the exercise requirements as they exceed the capacity of the disease-limited coronary circulation. At any rate, cases which showed the most marked deviations in the S-T intervals and in the T-waves, as well as the cases of conduction abnormalities, were all in the spontaneous group. The other group was by far the larger because of the large single series of thirty cases reported by Wood and Wolferth.[9] What deviations occurred in the artificially precipitated seizures not only were less acute in appearance but it happened that the cases which showed no deviations whatever all fell into this group.

We are reporting our case because it adds another record to the very small group of spontaneous attacks; because it has no predecessor in the literature that we have been able to locate showing the

classical coronary T-wave changes during an attack similar in conformation to those seen in acute myocardial infarction; because it illustrates forcibly the one electrocardiographic differential point between coronary thrombosis and angina pectoris, the fleeting duration; and, lastly, because it apparently reproduces in the human heart what has been seen experimentally in animal hearts, and in this way provides a connecting link in the evidence of the rôle that anoxemia plays in the pathogenesis of angina pectoris.

SUMMARY

1. The electrocardiographic changes in this patient during an attack of angina pectoris were characteristic of those often seen in acute myocardial infarction. After two minutes the curve had returned essentially to normal. The changes, we believe, were due to anoxemia of the cardiac muscle not involving the conduction paths.

2. We have been unable to find a similar case in the literature.

3. The changes are typical of those we have obtained in animal experiments with cardiac anoxemia; similar in conformation and as transitory.

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Department of Clinical Reports

CORONARY OCCLUSION DUE TO METASTASES FROM CARCINOMA OF THE BREAST*

Report of a Case Coming to Necropsy Five Years After Radical Mastectomy

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REPORT OF CASE

THE patient was a female seventy-five years of age who was first seen January 8, 1929. Her health in the past had been unusually good except for the fact that she had had a carcinoma of the right breast removed by radical resection in 1924, but since then frequent examinations had given no direct evidence of recurrence or extension of the malignancy. Her complaints when first seen were a dependent edema which had been present for a year or so, and a gradually increasing dyspnea, especially on exertion, during the last few weeks.

On examination she was found to be slightly underweight. Her blood pressure in millimeters of mercury was 130 systolic and 74 diastolic, there was no adenopathy palpable, and the scar of the previous mastectomy contained no nodules or indurated areas. There was a firm mass over the midportion of the sternum at the level of the third interspace which was attached to the skin as well as to the underlying tissues. The heart was not enlarged, its rhythm was regular, the rate was 90 beats per minute, and on auscultation no murmurs were heard. Examination of the lungs gave negative results. The liver could be palpated about 3 cm. below the costal margin, and on pressure it was found to be rather tender. There was a mild edema of both legs and ankles.

Laboratory Findings.—The urine showed slight traces of albumin along with varying numbers of pus cells in the urinary sediment. The concentration of the hemoglobin of the blood by the Dare method was 87 per cent, the red cells numbered 5 million, and the leucocytes 7,400 per cubic millimeter of blood. The electrocardiographic tracing showed inversion of the T-wave in the first lead but not in Leads II and III. An occasional extrasystole interrupted an otherwise normal rhythm.

Clinical Course.—The patient was afebrile at all times. On January 24, 1929, and again on February 6 the patient had an attack of severe dyspnea, cyanosis, and weakness, but recovered fairly well after rest and stimulation. The use of digitalis, euphyllin, and theophyllin produced no discernible improvement, and on February 11, the patient died suddenly after a little exertion.

Autopsy.—The body was that of a fairly well-developed and well-nourished female 161 cm. in length and weighing 140 pounds (63.6 kilos). There was a small amount of edema of the feet and ankles, extending about halfway to the knees. There was a scar over the right thorax extending toward the axilla, resulting from the previous radical amputation of the breast. This scar was soft and presented no evidence of recurrence of the malignant process. Over the midsternum at the

*Presented before the Minnesota Heart Society, April, 1929.

level of the third interspace there was a subcutaneous nodule measuring 3 cm. in diameter and quite firm to palpation. This was removed for microscopic study. Examination of the contents of the abdominal cavity gave essentially negative results.

Both pleural cavities contained a quantity of clear, straw-colored fluid, that on the right measuring about 1500 c.c. and on the left 500 c.c. No adhesions were present between the pleural surfaces, and there were no nodules to be found. The pericardial sac was filled with about 800 c.c. of a similar type of fluid. The heart weighed 300 grams and was grossly normal in appearance. Examination of the course of the coronary arteries revealed an unusual finding. The left coronary especially, but also the right, was marked by a pearly white, raised, hard, infiltrating tissue which was almost cartilaginous to palpation, and which extended in variable degrees throughout the length of both arteries down to the small branches. The lumen of these arteries was not completely occluded, but in several areas there were arteriosclerotic patches which practically obstructed the flow of blood. No infarction of the heart muscle could be made out, although the entire myocardium was definitely softened. There were a few arteriosclerotic patches throughout the aorta. Several lymph nodes of the mediastinum were enlarged, and their cut surfaces revealed a dense pearly white, cartilaginous substance identical to that surrounding the coronary arteries, and likewise identical to that found on section of the skin nodule over the sternum. The remainder of the autopsy was without relevant findings. The head and neck were not examined.

Sections for microscopic study were taken from a number of areas along the course of the coronary arteries, and these showed infiltration of the epicardium about the vessel with adenocarcinomatous tissue which extended in several places a short distance into the myocardium, but this was only to a slight degree. The vessel wall itself was not involved in the process, but its lumen was markedly compressed, especially in areas thickened by arteriosclerotic patches. Microscopically the mediastinal nodes and the subcutaneous mass overlying the sternum showed the same adenocarcinomatous structure.

COMMENT

Undoubtedly in this case death was caused by an unusual sequence of events which terminated in occlusion of the coronary arteries. Late metastases from the adenocarcinoma of the breast, which had been removed by radical resection five years previously, appeared in a very unexpected location, namely, in the epicardium surrounding the coronary arteries. The mechanism of the localization of the metastases in this particular place is obscure, although unquestionably the blood stream was the medium through which the transfer of malignant cells took place. While in this person a certain amount of arteriosclerotic thickening could be expected due to her age, yet it probably would have caused few symptoms. However, with the added insult of gradual obstruction of the arterial supply of blood to the heart from the carcinomatous tissue, symptoms and signs of cardiac failure became more and more prominent until death supervened.

Metastatic tumors of the heart, of various types, while they are comparatively rare, have been reported from time to time, but none has been found which corresponds to the type of lesion described in this case.

PAROXYSMAL COMPLETE AURICULO-VENTRICULAR HEART-BLOCK

A Case Report

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WE ARE reporting this case of complete A-V heart-block with Adams-Stokes syndrome because of the following unusual features: (1) The block occurred in paroxysms, the conduction time between attacks being normal. (2) During the presence of the abnormal mechanism the ventricular rhythm was grossly irregular and the ventricular complexes were aberrant and of several different forms. (3) After a period of several months, during which time the patient developed an acute streptococcic sore throat followed by an empyema, the attacks ceased and have not recurred after a period of over two years.

CASE HISTORY

H. B., a single, white laborer, aged forty-three years, was seen first on February 20, 1931, in consultation with Dr. R. L. Sands, who had been called because of a fainting spell accompanied by a convulsion. At the time of our examination the patient had recovered; the cardiac rhythm was regular, the pulse 80 per minute.

During the preceding month the patient had experienced repeated peculiar spells, which began with pounding of the heart, followed shortly by "hot flashes," dizziness, ringing in the ears, weakness, and profuse sweats. On several occasions, during the more prolonged attacks, he had lost consciousness and had been told by his relatives that he had had convulsions. At the first warning of an impending attack he would lie or sit down and as a consequence he had never fallen during an attack. The attacks came without apparent cause and occurred irregularly. On some days he had repeated short seizures and then would go for several days to a week without any trouble.

The family history was irrelevant. He denied all past illness except an occasional sore throat and a severe leg infection several years ago. He was well developed and nourished. The tonsils were infected *grade two.* The lungs were negative. The apex-beat was just within the midclavicular line; the area of cardiac dullness was not increased. A harsh systolic murmur replaced the first sound at the apex and was transmitted into the axilla. Systolic blood pressure was 130, diastolic 80. The palpable peripheral arteries were not sclerotic. Pressure over the vagi did not influence the heart rate.

A seven-foot x-ray film (Fig. 1), taken several days later, showed a heart shadow of normal size and contour.

An electrocardiogram (Fig. 2) revealed a normal rhythm and a P-R interval of 0.18 seconds.

The patient remained symptom-free until March 1, when he again became unconscious and had convulsions. When seen one hour later, he was conscious but

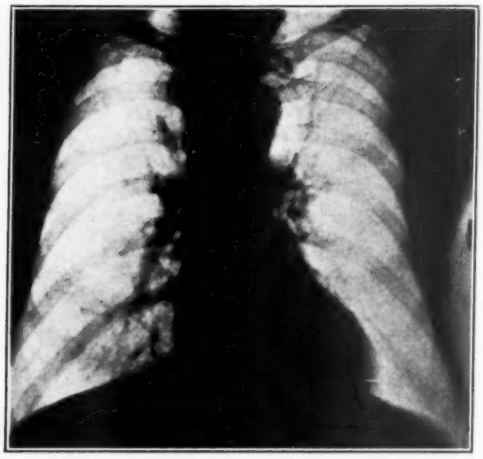

Fig. 1.—A seven-foot film of chest taken on Feb. 23, 1931.

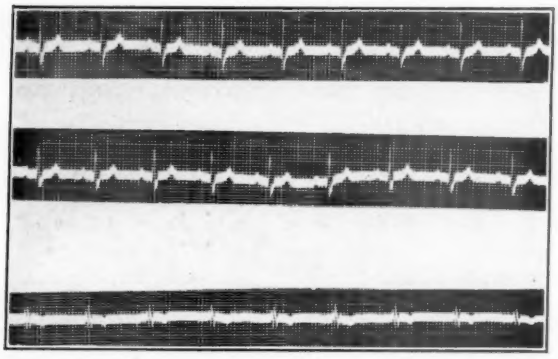

Fig. 2.—Electrocardiogram taken on Feb. 23, 1931. Normal sinus rhythm. P-R interval is 0.10 seconds.

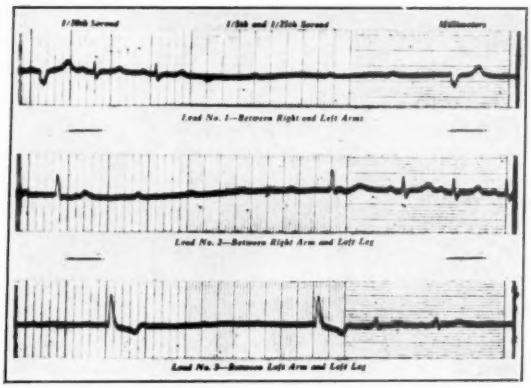

Fig. 3.—Electrocardiogram taken on March 1, 1931. Complete A-V heart-block. Ventricular complexes are aberrant, of several different forms, and are irregular.

would answer questions only in monosyllables. He was pale and frightened. There was no dyspnea. The radial pulse was slow and irregular. On auscultation of the precordium one could hear a regularly recurring sound at a rate of 90 per minute due to auricular contraction; the ventricular contractions, accompanied by a systolic murmur, were slow and extremely irregular. During one quarter-minute period the ventricles would contract once, in the succeeding similar period, there would be four or five beats. The average ventricular rate was 19 per minute. An electrocardiogram (Fig. 3) was obtained. During the night, atropine, caffeine, and adrenalin were given with no change in the condition. The next day a normal rhythm was resumed.

On March 5, the patient was sent to the hospital for observation. For a period of ten days the rhythm was normal; the pulse ranged from 68 to 88. A two-hour

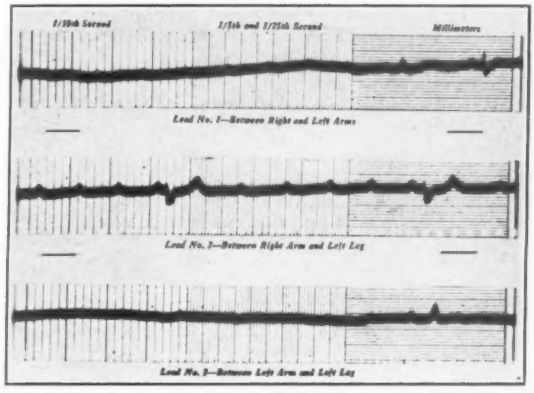
1/10th Second
1/5th and 1/25th Second
Millimeters
Lead No. 1—Between Right and Left Arms
Lead No. 2—Between Right Arm and Left Leg
Lead No. 3—Between Left Arm and Left Leg

Fig. 4.—Electrocardiogram taken during one of the paroxysms occurring while the patient was in the hospital.

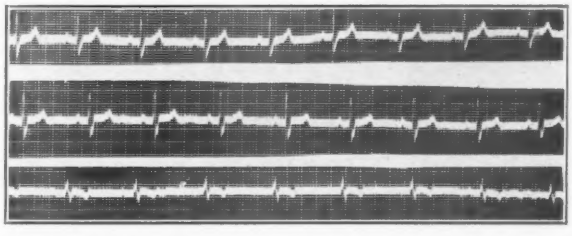

Fig. 5.—Electrocardiogram taken on April 12, 1932. Normal sinus rhythm. P-R interval is 0.16 seconds.

temperature curve showed an absence of fever. A daily leucocyte count was normal. He complained of vague pain in the legs and unlocalized abdominal distress. The Wassermann reaction was negative. Urinalysis was negative.

On March 14, the patient complained suddenly of "hot flashes" and dizziness. His pulse rate dropped to 17 per minute and he became stuporous. He had several epileptiform attacks lasting approximately one minute. The physical findings were, in all respects, similar to those found during the former attack. Atropine sulphate, gr. $\frac{1}{30}$, hypodermically, was without effect. After three hours normal rhythm was restored. Later in the day a similar episode occurred which lasted for only one-half hour.

During the following two weeks the periods of abnormal rhythm recurred daily. The duration of the attacks gradually lengthened until the block was present most

of the time. During the first few days adrenalin would raise the pulse rate and relieve the symptoms but later it seemed to lose its efficacy. Barium chloride and thyroid extract were tried without avail.

On April 2, the patient developed an acute tonsillitis and the temperature rose to 103° F. The pulse rate remained constantly below 40 in spite of the elevated temperature. On April 12, the patient complained of pain in the right axilla, the temperature rose to 104° F., and a pleural rub was heard. On April 24, 800 c.c. of serosanguinous fluid was aspirated from the right pleural sac. The rhythm at this time became normal and remained so. On April 26, a rib was resected and a drainage tube inserted. He experienced considerable respiratory difficulty from the open pneumothorax during the first few days. Convalescence was slow but the patient was discharged without drainage on June 20.

The patient was seen last on April 12, 1933. He had remained entirely symptom-free. His physical findings were essentially the same as when discharged from the hospital. An electrocardiogram (Fig. 5) showed a P-R interval of 0.16 seconds. He had no symptoms of congestive heart failure.

DISCUSSION

The most frequent causes of heart-block are acute infections, notably rheumatic fever and diphtheria, arteriosclerotic heart disease, syphilis, and digitalis intoxication. Overactivity of the vagus often plays an important rôle in precipitating a complete dissociation, as is evidenced by the occasional return of a normal mechanism under the effect of atropine. This is more apt to occur in those cases which result from digitalis. Pardee states that "it is extremely doubtful if it (vagus activity) ever produces more than an accentuation of a condition fundamentally due to disease." That a favorable response to atropine does not exclude organic disease is shown by a case reported by Carter and Dieuade in which a return of a normal rhythm occurred as a result of atropine administration and yet necropsy showed a badly diseased bundle.

It is obvious that a lesion of the bundle of His, whether inflammatory, degenerative, or toxic, may resolve and leave a functionally intact bundle. The not infrequent temporary presence of a block, especially of minor grade, seen during the course of acute infections or after a coronary occlusion demonstrates this fact. The repeated attacks of complete block with a normal conduction time in the interim as seen in this patient are more difficult to explain. We do not feel that they were due to vagus activity alone, especially in view of the fact that atropine was ineffectual and that vagus pressure between the attacks failed to slow the pulse rate.

Carter and Dieuade in attempting to explain a similar case remarked that "there probably exists a large reserve in the conduction capacity of the bundle which may be seriously encroached upon before conduction is measurably impaired; some subtle circulatory or temporary vagal action may result in a failure of the few remaining intact fibers to transmit impulses." In view of the mitral valvulitis in this patient

we feel that he had a rheumatic lesion of the conduction system. A flare-up of this smoldering inflammation would account for the attacks, while its subsidence could explain their cessation.

The idioventricular rhythm which becomes established in complete A-V dissociation is usually slow and regular. Many of the standard textbooks on cardiology fail to mention the fact that the ventricular rhythm in complete block may be irregular. Certainly a gross irregularity is most unusual. Pardee states "that occasionally with complete block the ventricular complexes are aberrant and when this occurs with a regular intersystolic interval it is considered as being due to a variable conduction through one or other bundle branch of an impulse arising in the A-V node. If, however, there is also present a slight coincidental irregularity of ventricular rhythm, both variations are considered as due to a varying site of impulse formation." In the present case, the gross irregularity and change in the form of the QRS is best explained as being due to the formation of impulses at several different sites.

SUMMARY

A case of recurring or paroxysmal complete A-V heart-block is reported. The symptoms associated with the paroxysms constituted the patient's only complaints. He had signs of a mitral valvulitis but had never had any symptoms of congestive heart failure. During the paroxysms the ventricular rhythm was grossly irregular and the ventricular complexes in the electrocardiogram were aberrant and of several different forms. The cause of the block was considered to be a chronic rheumatic myocarditis.

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Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram, New York, Paul B. Hoeber, Inc.

Carter, Ed. P., and Dieuade, F. R.: Bull. Johns Hopkins Hosp. 34: 401, 1923.

Department of Reviews and Abstracts

Selected Abstracts

Wiggers, C. J., and Cotton, F. S.: Studies on the Coronary Circulation. I. The Coronary Pressure Pulses and Their Interpretation. Am. J. Physiol. **106**: 9, 1933.

Pressure pulses were simultaneously recorded from the aorta and either from the central end or from a lateral branch of the anterior descending ramus of the left coronary artery of the dog. Calibrated optical manometers designed and described by one of the authors were used. They had a high figure of merit when tested under conditions of actual use. A technic was developed by which artefacts due to motions of the heart were eliminated.

Such simultaneous records give no indication that the pressure relations or form of the coronary pressure pulse are modified by any factor except the pressure changes in the aorta. The minor changes noted are such as occur in other branches of the aorta. The conclusions of Hochrein and Gros, that in addition heart rate, capacity and elasticity of the aorta, eddies and friction due to an unusually well-developed intima are not supported by these studies. The authors regard these conclusions invalid for (1) comparisons of coronary and carotid pulses do not serve for the study of the problem because the contour and pressure values of the latter differ essentially from those in the aorta, and (2) evidence indicates that the records on which conclusions are based contain many artefacts and hence do not picture the correct form of pressure fluctuations either in the coronary or carotid arteries.

Haney, Hance F., Borman, M. C., and Meek, Walter J.: The Relation Between the Position of Experimental Myocardial Lesions in the Dog and the Changes in the RS-T Segment of the Electrocardiogram. Am. J. Physiol. **106**: 64, 1933.

The changes in the level of the R-T and S-T segments of the electrocardiogram were studied following the production of myocardial lesions in the dog. The lesions were produced by means of radon implants. An attempt was made to correlate the position of the lesion with the changes in the level of R-T and S-T.

Lesions on the anterior surface of the left ventricle consistently produced changes of the T_1 type. Lesions on the posterior surface of the left ventricle resulted in changes of the T_3 type in 6 of a total of 7 dogs studied. One showed no change.

Lesions on the anterior surface of the right ventricle resulted in changes of the T_1 type in 5 of 8 dogs studied. The remaining 3 showed no change from the normal. Lesions on the posterior wall of the right ventricle resulted in changes of the T_3 type in 4 dogs, the T_1 type in 2 dogs and no change in 1.

Bowman, James E.: Blood Pressure in the Newborn. Am. J. Dis. Child. **46**: 949, 1933.

The literature on arterial blood pressure in the newborn is reviewed.

The tension in a group of 100 babies was recorded for the first four days of life, averaging successively 55 systolic, 38 diastolic; 60 systolic, 41 diastolic; 60

systolic, 42 diastolic, and 60 systolic, 44 diastolic. The determinations were made with the Pachon oscillometer, with a 5 by 20 cm. cuff placed about the right leg. In general, the systolic blood pressure is higher in the babies of greater weight at birth, while the diastolic varies little. There was little difference in the blood pressure of 15 babies of the same weight group (from 7 to 8 pounds) born spontaneously.

Interesting observations were noted on comparison of tension before and after drainage of spinal fluid in 4 infants with cerebral hemorrhage.

Bohning, Anne, Jochim, Kenneth, and Katz, Louis N.: The Thebesian Vessels as a Source of Nourishment for the Myocardium. Am. J. Physiol. **106:** 183, 1933.

Bismuth was conveyed from the heart chambers into the coronary sinus blood in the beating heart with the coronary circulation isolated from the systemic, in seven out of ten experiments. In two of these experiments, the possibility of any connection between the systemic and the coronary blood by means of extra cardiac anastomoses was excluded by perfusing directly into the coronary arteries.

In preparations of beating hearts with a completely isolated coronary circulation, a suspension of a pure culture of killed bacteria was injected into the superior vena cava. The same bacteria could be demonstrated in the sinusoidal spaces, the capillaries, the small intramural arteries and veins, the superficial branches of the coronary arteries and veins, and also in the blood from the coronary sinus. These experiments, therefore, indicate that the thebesian vessels do form a pathway in the functioning heart by which blood can be conveyed from the heart chambers to the intramural coronary vessels.

Under normal conditions, the amount of blood conveyed by this pathway appears to be comparatively small but in some pathological conditions, where the coronary arteries are occluded, enough blood may find its way into the coronary capillaries to aid appreciably in the nourishment of the heart.

Wright, Irving Sherwood, and Duryee, A. Wilbur: Human Capillaries in Health and in Disease. Arch. Int. Med. **52:** 497, 1933.

In this article an endeavor has been made to review the present knowledge concerning human capillaries in health and in many specific diseases. The field is relatively undeveloped, and it is believed that present theories will be discarded in the near future and that many additional pathological processes will be studied from the point of view of the capillaries and circulation. The authors have used an apparatus devised by them and previously described.

In the first section of the paper there is a full discussion of the anatomical appearance and the physiological function of the normal capillaries. In the second section, capillary changes in various disease conditions are described and discussed.

Stainsby, Wendall J., and Nicholls, Edith E.: The Clinical Significance of the Erythrocytic Sedimentation Test in Rheumatoid Arthritis. J. Clin. Investigation **12:** 1041, 1933.

The erythrocytic sedimentation test was performed on five hundred and ninety-seven patients with rheumatoid arthritis in order to determine its significance in this disease. The results of the investigation indicate that the corrected sedimentation index is a reliable criterion of the activity or severity of the arthritic process at the time of testing, and that any fundamental change in the clinical condition produces immediate corresponding change in the sedimentation rate. Patients with greater degrees of joint involvement and a longer disease duration

have higher sedimentation rates on the average, than those with less joint involvement and shorter disease duration. Considerable variation occurs, however, in individual cases.

The observation that the average sedimentation rate progressively increases with advancing age periods is of interest. This phenomenon appears to be due primarily to the increasing accumulation of patients with severe arthritis in whom the disease began at some earlier age.

From a study of seasonal variations in the sedimentation rate over a long period, suggestive evidence was deduced that on the average the rate was higher in winter than in summer, while spring and autumn occupied intermediate positions. No relationship was found between the sedimentation rate and the streptococcus agglutination reaction.

With the above-mentioned information at hand, it seems justifiable to discuss the practical importance of this test. In the past, physicians treating arthritis have been greatly handicapped by lack of means for estimating the results of their therapy. The sedimentation test appears to supply this widely felt need, as it is a reliable measuring rod of the activity or severity of the arthritic process. By repeating this test at regular intervals the progress of the patient may be determined. The sedimentation test provides a ready aid for correctly estimating the value of various treatments proposed for rheumatoid arthritis.

Struthers, R. R., and Bacal, H. L.: Determination of the Activity of Rheumatic Infection in Childhood. Canad. M. A. J. **29:** 470, 1933.

It is concluded after observations on thirty-one cases of rheumatic infection that uncomplicated rheumatic fever shows a high sedimentation rate, usually a leucocytosis of 12,000 to 15,000, fever, approximation of the sleeping and waking pulses during the period of fever, and loss of weight. All these evidences of activity tend to subside with the clinical evidence of subsidence of the infection. Rheumatic fever with carditis shows a sedimentation rate which requires a period of months to return to normal, and hence is probably the most delicate of these tests in the determination of activity of rheumatic infection, except in the presence of congestive failure with edema when it falls rapidly to levels below the normal and is of grave prognostic import.

It was found that chorea without carditis shows no alteration in the total white blood cell count, sedimentation rate, or fever. When the chorea is complicated with carditis even in the absence of fever, it shows the same changes in these criteria as does rheumatic fever with carditis, except the absence of leucocytosis.

Wilkins, Walter E., and Cullen, Glenn E.: Electrolytes in Human Tissue. III. A Comparison of Normal Hearts With Hearts Showing Congestive Heart Failure. J. Clin. Investigation **12:** 1063, 1933.

The right and left ventricles of 17 human hearts were analyzed for water, phosphorus, sodium, potassium, magnesium, and calcium. Of these hearts, 5 were normal, 4 were from persons who had cardiac disease but who died from other causes, and 8 were from persons who died with congestive heart failure.

The water content of the diseased right ventricle tends to be slightly higher than that of the left ventricle. The water content of both ventricles of hearts from persons who died with congestive heart failure was found to be increased. The normal left ventricle contains more total phosphorus and more potassium than the right. Both ventricles of diseased hearts showed a decrease in total phosphorus and potassium. The normal right ventricle contained more sodium

than the normal left ventricle. Sodium was increased in both ventricles of persons who died with congestive heart failure. Usually the right ventricle contains a slightly higher concentration of calcium than does the left ventricle. No consistent variations were found in the calcium content of the ventricles of persons who died with congestive heart failure. Both the normal and diseased left ventricles were richer in magnesium than the corresponding right ventricles. Both ventricles of the diseased hearts showed a diminution in magnesium.

The sums of the individual bases when calculated in milliequivalents per kilo of tissue water show that the two ventricles do not differ essentially in their content of total base. The potassium-sodium ratio in the normal left ventricle is higher than in the normal right ventricle. Both ventricles of the diseased hearts showed a decrease in this ratio. The phosphorus-potassium ratio was somewhat higher in the right ventricle than in the left. The diseased hearts had nearly the same phosphorus-potassium ratio in both ventricles as did the normal hearts, showing that the former had a proportionate decrease in phosphorus and potassium.

Harrison, William Groce, Jr.: The Cisternal Pressure in Congestive Heart Failure and Its Bearing on Orthopnea. J. Clin. Investigation **12:** 1075, 1933.

A study was made of the cisternal pressure, the lumbar spinal fluid pressure, the systemic venous pressure, the vital capacity, the arterial blood pressure, and the pulse and respiration rates in the recumbent and upright positions in five patients without cardiac disease and in five patients with congestive heart failure.

The arterial blood pressure and pulse rate were usually slightly greater in the sitting than in the prone position, but, in general, the blood pressure and the pulse and respiration rates showed no marked consistent changes with position in either group. The systemic venous and lumbar spinal fluid pressure were greater in the sitting than in the prone position in each subject and were much greater in each position in the patients with congestive heart failure than in the patients without cardiac disease. The vital capacity was greater in the sitting than in the prone position in both groups of cases, and the percentile increase of vital capacity with change in position was greater in the patients with cardiac disease.

The cisternal pressure was much greater in each position in the group with congestive heart failure than in the other group. The cisternal pressure was much less in the upright than in the recumbent posture in each case, and this difference in cisternal pressure between the two positions was much greater in patients with congestive heart failure than in those without cardiac disease. As a result of these observations, it is believed that in addition to the increase in vital capacity, the diminished cisternal pressure is an important factor in producing the relief from dyspnea obtained in the sitting position. The mechanism of this effect is, as yet, unknown.

Seham, Max, and Hilbert, Eunice H.: Muscular Rheumatism in Childhood. Am. J. Dis. Child. **46:** 826, 1933.

The results of a study of thirty-five children suffering from what are predominately chronic muscular pains are presented in this paper. No evidence was found to substantiate the old idea that normal growth causes chronic muscular pains. It is believed that the term "growing pains" is a misnomer and should be discarded. Chronic pains in the muscles which can be differentiated from chronic fatigue and definite orthopedic disorders are probably the result of a chronic infection.

Twenty-one per cent of 208 children from eight to fifteen years of age gave histories of having muscular pains over a period of three months or more. The age incidence of these muscular pains was practically the same as that for all other forms of rheumatism. It was no higher during puberty than at any other period.

There was a significant relation between muscular pains and inadequate sleep and fatigue.

Systolic murmurs developed in 30 per cent of the children who had continuous fever and in only 19 per cent of the children who were afebrile. Of these, 11 per cent acquired chronic mitral endocarditis. The average sedimentation rate at the end of one hour for the normal group was 5.9 mm.; for the convalescent rheumatic persons and those in whom the disease was inactive, 10 mm.; for those with muscular rheumatism, 8.7 mm.; and for those with chorea, 11 mm. The average streptococcic agglutination titer for the normal group was 1:160 and for the children with muscular rheumatism, 1:1,500. In the normal group, 92 per cent of the titers were below 1:200, whereas, in the abnormal group only 7 per cent were below 1:200.

Hoyle, Clifford: Pituitary Secretion in High Blood Pressure. Quart. J. Med. 2: 549, 1933.

It is not possible to detect pituitrin in normal unconcentrated human cerebrospinal fluid obtained by lumbar puncture, even if sufficient be taken to make it probable that it comes from the cerebral cisterns.

Patients with essential hypertension or with hypertension associated with chronic renal insufficiency do not usually show an excess of pituitrin in such cerebrospinal fluid. Pituitrin may be detected occasionally, but even then only minute traces are found. The absence of a significant increase is held to be strong evidence that hyperpostpituitarism is not concerned as an etiological factor in these varieties of hypertension.

Wood, Francis Clark, Bellet, Samuel, McMillan, Thomas M., and Wolferth, Charles C.: Electrocardiographic Study of Coronary Occlusion. Further Observations on the Use of Chest Leads. Arch. Int. Med. 52: 752, 1933.

Thirty-six cases of acute coronary occlusion are reported in which chest leads as well as limb leads were used in the electrocardiographic study. Three chest leads were used: Lead IV, from the lower precordium to the angle of the left scapula; Lead V, from the lower precordium to the left leg, and Lead VI, from the angle of the left scapula to the left leg.

The exact location of the anterior chest electrode is important in determining the contour of the electrocardiogram. This has not been true in the case of the posterior electrode. The methods used in taking chest leads and the normal findings in Leads IV, V, and VI are discussed.

Certain variations which have been seen in pathological cases without acute cardiac infarction are described. Deviations in the RS-T interval may occur in chest leads in the absence of acute coronary occlusion.

An electrocardiographic analysis of our 36 cases shows that 31 of them tend to fall in one or the other of two groups, termed for convenience Groups A and B.

Group A consists of 19 cases. Examples of this group are shown in charts. Four cases in this group which have come to necropsy have shown occlusion of the left anterior descending coronary artery, with infarction of the anterior surface of the left ventricle, usually including the apex and the anterior half of the interventricular septum.

Group B consists of 12 cases. Examples of this group are shown in charts. The data at hand suggest that these are cases of infarction of the posterior wall of the left ventricle due to occlusion of the right coronary artery.

When chest leads as well as limb leads were used, all but one of the cases of acute coronary occlusion showed electrocardiographic evidence of the lesion during the first few days. The absence of deviations of the RS-T interval in all six leads renders the diagnosis of recent coronary occlusion quite unlikely.

Certain characteristic alterations produced in the QRS complex as a result of coronary occlusion tend to persist. Thus, several months after coronary occlusion has taken place, the findings in the QRS complexes and T-waves may point to the nature of an antecedent attack. There are certain indications that the symptoms of a posterior infarction when compared with those of an anterior one, are often less dramatic and less prolonged; that the immediate prognosis is less grave, and that the subsequent recovery of adequate cardiac function is apt to be more rapid and more complete.

Landis, Eugene M., and Gibbon, John H.: A Simple Method of Producing Vasodilatation in the Lower Extremities. Arch. Int. Med. 52: 785, 1933.

The forearms of patients were immersed in warm water (43° to 45° C.) for thirty-five minutes in order to produce vasodilatation in the lower extremities. This vasodilator response was studied in 24 patients two showed clinical evidence of peripheral vascular disease.

In 7 patients with pain, coldness, or cyanosis of the lower extremities, the temperature of the toes rose to levels above 32° C. This normal response definitely excluded the possibility of obliterative structural disease of the arteries as a cause of the diminished flow of blood in the lower extremities.

Four patients with thromboangiitis obliterans or arteriosclerosis involving the lower extremities showed varying grades of organic occlusion and spasm when tested by this method.

In 8 of the 13 patients who failed to show the normal vasodilator response to warming the forearms, the results were compared with those obtained by some other method of producing vasodilatation, including the intravenous injection of typhoid vaccine, the use of spinal anesthesia, and anesthetization of the posterior tibial nerve. In 7 of the 8 patients the clinical interpretation of the findings by both methods was the same. In 1 patient with arteriosclerosis warming the forearms failed to produce a vasodilator response, whereas anesthetization of the posterior tibial nerve showed that the vessels were capable of limited dilatation.

Three patients with acrocyanosis of the lower extremities showed abnormal vasodilator responses to warming the forearms, though anesthetization of the posterior tibial nerve produced complete, but rather delayed elevations in skin temperature. These findings are discussed with reference to the mechanism of the diminished flow of blood in acrocyanosis.

Warming the forearms in water at a temperature of from 43° to 45° C., for thirty-five minutes is a simple and entirely unobjectionable method of producing vasodilatation in the lower extremities. If the surface temperature of the toes rises above 31.5° C., significant obliterative structural disease of the arteries of the lower extremity is definitely absent. If the surface temperature fails to rise to this level, organic arterial obstruction is probably present. With controlled room temperature, the approximate grade of the organic obstruction is indicated by the difference between 31.5° C., and the maximum temperature reached. For absolute certainty in the diagnosis of organic arterial obstruction, the abnormal

vasodilator responses obtained by warming the forearms should be confirmed by some other method of producing peripheral vasodilatation.

Laws, Clarence L., and Levine, Samuel A.: Clinical Notes on Rheumatic Heart Disease With Special Reference to the Cause of Death. Am. J. M. Sc. 186: 833, 1933.

One hundred and forty-eight cases of rheumatic heart disease were studied to ascertain the cause of death. It was found that congestive heart failure accounted for only 33.1 per cent of the fatalities, acute rheumatic carditis for 23 per cent, peripheral emboli and thromboses for 11.5 per cent, subacute bacterial endocarditis for 29 per cent, and 3.4 per cent died of miscellaneous cardiovascular accidents, such as angina pectoris or acute pulmonary edema.

The groups of congestive failure and emboli and thromboses were the oldest, subacute bacterial endocarditis a little younger, and acute rheumatic carditis the youngest.

Those that had aortic valvular disease alone were the oldest (52.5 years). The mitral cases came next (42.8 years) and the patients with combination of aortic, mitral, and tricuspid were youngest (30 to 35 years).

There were more than twice as many females as males dying of acute rheumatic carditis, the relation was reversed in the group dying of emboli and thromboses, and the proportion was 3 to 2 on the side of males in the subacute bacterial endocarditis group.

A past history of rheumatic fever or chorea was not found with equal frequency among the various groups. While the authors believe that stenosis of any of the valves is, except in rare instances, of congenital heart disease, practically invariably due to rheumatic infection, the multiform character of the early illness prohibits obtaining a positive past history in many instances. The greater the number of valves involved, the more frequently was a positive past history obtained. This is true for two reasons: such patients are more apt to have had more than one infection and they die at a younger age, so that the early illnesses are not forgotten. This explains why patients with aortic stenosis who die at an old age less frequently have a positive past history.

In speaking of valvular lesions in this review, except for those patients dying of subacute bacterial endocarditis, we mean stenosis to a greater or lesser extent. A striking finding was the great frequency of involvement of the aortic and tricuspid valves. When the tricuspid valve was involved, the mitral was always diseased as well, and frequently the aortic.

Auricular fibrillation was almost invariable in the emboli and thrombi group, very common in those dying of congestive heart failure, much less common in the acute rheumatic carditis group, and practically absent in those who died of subacute bacterial endocarditis. The presence of mitral stenosis is the most common accompaniment of auricular fibrillation, although this irregularity occurs occasionally in patients who have only aortic stenosis.

The average weight of the heart of those dying with congestive failure was 617 gm., of acute rheumatic carditis or emboli and thromboses about 550 gm., and of subacute bacterial endocarditis 449 gm. The average weight of the heart in cases of aortic stenosis was 669 gm., of mitral stenosis 474 gm., and of both 663 gm. When the tricuspid was involved in combination with other valves, the average weight was about 550 gm. The presence of adhesive pericarditis increased the average weight by about 120 gm. The average weight in 43 patients with adhesive pericarditis was 654 gm., and in 62 patients with a normal pericardium was 534 gm.

Pericarditis with or without adhesions was less frequent in the older patients. It was most common in the group with acute rheumatic carditis, fairly frequent in those with congestive heart failure, and very rare with subacute bacterial endocarditis.

Otto, Harold L., Gold, Harry, and Messeloff, Charles R.: Studies on Digitalis in Ambulatory Patients With Cardiac Disease. V. Further Observations on the Nature of the Cumulation of Digitalis. Arch. Int. Med. **52**: 725, 1933.

The present study was undertaken to ascertain the curve of the cumulation of digitalis in patients with a regular sinus rhythm without heart failure, the criteria being changes in the P-R interval and in the T-wave which may, under these conditions, be ascribed only to a direct action of the drug and which cannot be produced as indirect effects of an improved state of the general circulation.

Many difficulties encountered in the course of the study reduces the number of successful experiments to such an extent that on only 12 of the 75 patients was it possible to carry out observations that were adequate for the purpose of the investigation.

It was possible to demonstrate the following facts:

1. One daily dose of digitalis was insufficient to produce the full effects seen after the continued administration of the drug.

2. With the continued daily administration of digitalis a curve of increasing intensity of effects resulted.

3. After a time, a level was reached beyond which the effects did not increase in intensity.

4. This level was maintained for a length of time sufficient to insure that the dose could not produce greater effects by any criterion of the action of digitalis.

5. A larger dose was capable of producing greater effects, which indicated that the criteria employed were sufficiently sensitive to reveal the presence of more digitalis.

It is believed that the experiments carried out in this study confirm the conclusions of Gold and deGraff, that patients do not excrete a fixed quantity of digitalis daily, but one that varies with the amount present in the body.

Gilchrist, A. Rae: The Action of Adrenalin in Complete Heart-Block. Quart. J. Med. **2**: 499, 1933.

Twelve cases of complete heart-block have been tested with repeated subcutaneous doses of adrenalin in an attempt to discover the factors which govern the response of the heart to this drug.

After a subcutaneous dose, the drug comes into action with surprising rapidity. Acceleration of auricles and ventricles may occur within two to four minutes of the injection. The amount of ventricular acceleration induced bears a striking relationship to the rate existing immediately before the injection. High initial rates are followed by little or no gain in rate, slow rates by pronounced acceleration. This means that the state of the heart at the time of the drug's administration determines the heart's response.

By plotting the observed increment against the corresponding initial rate, it is found that for a group of 8 cases the reaction approximates to an almost perfect series of decreasing exponentials for increasing ventricular rates.

Within a certain range of dosage, the amount of adrenalin injected makes little or no difference to the ventricular response at a given ventricular rate. The optimum response to 0.5 c.c. adrenalin for various initial rates has been

calculated and compared with the reaction observed after doses of 0.25, 0.75, and 1.0 c.c. in the same subjects. The gain in rate after these doses is to all intents similar to that recorded after 0.5 c.c. This implies that the response of the heart is determined, not by the size of a dose in the usual therapeutic range, but by the rate of the heart existing at the time of the injection. In other words, for a given initial rate 0.25 c.c. of adrenalin will produce as much acceleration as a dose four times that amount.

This phenomenon is discussed in the light of the known laws which govern enzyme action. The independence of the size of the dose and the response recorded, suggests that a surface action is involved and that adrenalin is being adsorbed on some (? enzyme) surface, as an essential condition of the action.

The observation that the initial rate determines the degree of acceleration finds support in blood pressure studies. Lyon has suggested that the reaction to adrenalin obeys Weber's law, in that the amount of elevation in the systolic blood pressure, after uniform doses of adrenalin, depended upon its level at the moment of the injection.

It has not been found possible to demonstrate as close a correlation between the initial auricular rate and its increment after adrenalin as that observed in the case of the ventricles. The auricular response is modified to some extent, particularly in those cases in which the magnitude of the ventricular response is maximum, that is, when the initial ventricular rate is relatively low.

It would appear probable that reflex vagal influences, induced by a marked ventricular reaction, limit the auricular response. The amount of limitation is apparently determined largely by the initial ventricular rate.

The course of the reaction to a subcutaneous dose of adrenalin varies as much in complete block as it does in the normal beating heart. The maximum auricular and ventricular reactions are not necessarily synchronous. As a general rule, the auricles attain to the height of their reaction before the ventricles have completed their acceleration. An increased frequency of both chambers of the heart persists after the blood pressure rise has returned to its preexisting level. No untoward symptoms resulted from the use of the drug. Release from the block was not observed in any of the experiments performed upon these 8 patients.

Reactions differing from those just described were encountered in 4 patients. One of these cases was a man who suffered from intermittent complete block. Tested with adrenalin during complete block, no change in the rhythm occurred but a branch defect changed from one side of the heart to the other. Tested during 2 to 1 rhythm, complete block was induced. The direction of the main ventricular deflection varied according to the presence or absence of conduction through the main stem of the bundle. During half-rhythm the ventricular complex in Lead III was directed downward, whereas during complete dissociation its direction was upward. The fact that this man's heart was unduly susceptible to adrenalin suggests that in cases of intermittent complete heart-block, the temporary failure of conduction, leading to transient complete dissociation, may perhaps be associated with the formation within the body of some subtle and complex chemical substance analogous to adrenalin or adenosine.

Book Review

NOUVELLE MÉTHODE POUR LA DÉTERMINATION DES CHRONAXIES MYOCARDIQUE ET HISIENNE. By Adalbert van Bogaert, Sc.D., M.D., 191 pp. Poitiers. Société Française d'Imprimerie, 1933.

This monograph contains an account of observations on the excitability of the heart as determined by the chronaxie method of Lapicque. The purpose of the study appears to be the identification of certain cardiac disturbances from measurements of the "stimulability" of the heart in a special way that is designated as "longitudinal and transverse chronaxie."

The introduction contains a brief statement of the meaning of chronaxie (i.e., the intensity-duration characteristic of a stimulus) so that the reader unfamiliar with this method may gain an idea of the basic principles of the procedure. The main part of the work is presented under two divisions. The first deals primarily with experiments and arguments to establish the thesis of two distinct chronaxies in the heart (i.e., parts of the cardiac musculature having distinctly different excitabilities) and the second part contains an elaboration of this concept in an attempt to show that in certain disturbances, manifest by changes in the P-R and QRS intervals in the electrocardiogram, there is a prolongation of one of these chronaxie measurements.

The author makes use of the fact that the heart as a functional organ presents two structures histologically and physiologically, and upon this he postulates two chronaxies: one corresponding to the striated cardiac muscle and the other to the His-Tawara system. A large number of experiments are reported, covering a variety of procedures and pertaining to both the cold-blooded and the mammalian heart. From these one gleans that the basic things in the work probably center in the following considerations: (a) measurements of differences in excitability within the heart can be detected when the plane of the testing electrodes is transversely across the heart at the level of the A-V junction; (b) this chronaxie is two, three, or more times that for any other plane; and (c) this chronaxie measurement is definitely that of the His bundle system.

If one follows the experimental results as given, the fact seems convincing that a difference in chronaxie exists in a certain transverse plane of the heart, but doubt will come to the minds of those familiar with chronaximetry as to the interpretation of a causal relationship between this transverse chronaxie and the specialized tissue of the heart. Moreover, the extension of this line of reasoning to apply practically to the detection of changes in the conducting system from measurements made through the closed thorax, seems to be a generalization that will require additional evidence. Since the changes in the transverse ("His") chronaxie that are brought about with certain drugs (particularly ephedrine) to stimulate the usual type of disturbances over the conducting system are portrayed to a large extent by characteristic alterations in the electrocardiogram, the reasons for employing the chronaxie method carry less weight.

The monograph includes at the end a fairly complete bibliography and a helpful table of contents. The text contains many illustrations and a large number of concise tabulations which add greatly to the ease of following the argument and denote much care in its preparation.

D. J. E.

LA ANGINA DE PECHO. By Dr. Gregorio N. Martinez, Profesor de Clinica Medica de la Facultad de Cordoba. 278 pp. Buenos Aires, 1933, Humberto Andreetta.

In this volume of 278 pages the author attempts a systematic presentation of the subject of angina pectoris, using the term in its older and more general sense to include cases of coronary closure and cardiac infarction.

Much space is given to the subject of treatment, both medical and surgical, and there are included the condensed protocols of 49 personal cases. The book gives evidence of wide reading and is furnished with a full bibliography.

L. A. C.

ARRITMIAS. By Dr. Antonio Battro. 246 pp. Buenos Aires, 1933, Sebastian de Amorrurtu.

This volume, well printed and well illustrated, should be useful to the Spanish-speaking clinician. In addition to a discussion of the different arrhythmias, it includes the usual introductory chapters on general considerations and graphic methods. The author has succeeded in presenting established facts in a clear, concise form, providing a handbook suitable for the student or practitioner.

E. H.